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Thèse

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Pain perception in schizophrenia, and relationships between emotion and visual organization: is emotion flattened in patients, and how does it affect cognition?

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Résumé de thèse

La perception de la douleur dans la schizophrénie et la relation entre l'émotion et l'organisation visuelle de l'environnement: est-ce que les émotions sont perturbées chez les patients, et comment cela affecte-t-il la cognition?

La schizophrénie est une pathologie psychiatrique handicapante, qui touche 1% de la population. Elle est caractérisée par la présence de symptômes cliniques positifs et négatifs, ainsi que d'une désorganisation de la pensée et de l'action. Ces symptômes sont accompagnés de troubles neurobiologiques et cognitifs, lesquels traduisent souvent la désorganisation de la pensée. Ils sont observés jusque dans le domaine de la perception visuelle, avec des difficultés à regrouper les informations en un tout cohérent. En outre, une insensibilité à la douleur et aux émotions a été décrite chez les personnes atteintes de schizophrénie. Cependant, ces derniers troubles ont été peu étudiés, et l'impact des émotions sur le fonctionnement cognitif est mal caractérisé. Dans cette thèse, d'une part nous avons exploré la sensibilité à la douleur chez les patients schizophrènes, et d'autre part nous avons développé un paradigme destiné à explorer l'impact d'informations chargées émotionnellement sur les processus d'organisation en vision.

Les émotions jouent un rôle adaptatif dans certaines situations. Notamment en cas de danger, la perception des stimuli environnants doit se faire de manière efficace et le plus rapidement possible pour permettre l'identification du danger et pour y faire face. Cette réponse adaptative met en jeu différentes fonctions, comme l'attention ou la perception de la douleur, par exemple. De nombreuses études ont montré que les émotions positives ou négatives affectent la perception et le comportement. Les émotions positives inciteraient à explorer l'environnement, tandis que l'effet serait inverse concernant les émotions négatives. Aujourd'hui, l'homme n'est plus exposé aux dangers de la nature comme il l'était il y a des dizaines de milliers d'années, mais les émotions primitives ont persisté, et d'autres

émotions plus liées aux interactions sociales deviennent de plus en plus importantes. Ces dernières ont également un rôle adaptatif. Citons par exemple l'empathie, soit la capacité de reconnaissance des émotions chez autrui, ou encore l'embarras, qui peut survenir tel un malaise lors d'un «faux-pas social», et qui peut nous aider à corriger notre comportement.

Etant donné le rôle des émotions dans notre vie quotidienne, il est important d'étudier comment les troubles émotionnels provoqués par certaines maladies affectent les capacités d'adaptation. Dans la schizophrénie particulièrement, on retrouve des symptômes négatifs comme l'affect émoussé qui se traduit par un défaut d'expression émotionnelle chez les patients.

Pour tenter de comprendre l'interaction entre émotion et perception, nous avons exploré deux voies distinctes. Dans un premier paradigme, nous avons investigué l'effet de l'émotion sur les mécanismes d'organisation en perception visuelle. Cette partie de la thèse a nécessité de nombreuses expériences (16). La nouveauté du paradigme nécessite une argumentation solide et plusieurs contrôles, et nous avons choisi de réunir les expériences les plus importantes en un seul manuscrit, plutôt que de les présenter de façon séparée. Nous décrirons également dans la thèse les premiers résultats obtenus quand ce paradigme a été appliqué chez les patients. En parallèle, nous avons étudié la perception de la douleur chez les patients schizophrènes en considérant les différents mécanismes impliqués, dont l'émotion et les fonctions cognitives (attention, anticipation). Cette étude a requis un temps relativement long, avec des recrutements sur plusieurs sites, et un protocole lourd (EEG, stimulations douloureuses, prises de sang). Là encore ce travail est réuni au sein d'un manuscrit unique.

Etudes 1

La perception visuelle est un processus complexe nous permettant de percevoir notre environnement de manière cohérente, et ce rapidement. Or l'information visuelle est initialement décomposée au niveau du cortex visuel primaire en informations primitives (orientation, couleur, fréquences spatiales) et traitée par des neurones qui ont un très petit champ récepteur. Cette information doit donc être regroupée pour reconstituer, identifier, et organiser les objets de notre environnement. Ce processus de reconstruction de l'environnement comprend différentes étapes, et particulièrement les processus de groupement. Différents principes ont été mis en évidence : par exemple des stimuli qui ont la même forme ou la même couleur sont groupés automatiquement (fig. 1).

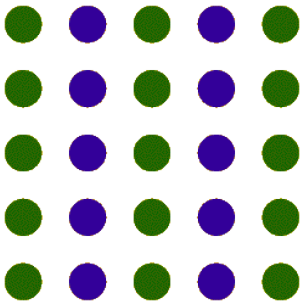

Figure 1. Exemple de groupement par couleur

Ces processus d'organisation visuelle guident l'exploration de l'environnement. En effet on explore plus facilement des informations qui appartiennent à un même objet (ou un groupe d'objets) que des informations qui sont localisées dans des objets (ou des groupes d'objets) différents. Un autre facteur important est l'émotion. Les informations émotionnellement chargées attirent l'attention et jouent également un rôle dans la manière dont nous explorons notre environnement, en facilitant la perception d'un objet ou en

jouant un rôle distracteur. L'influence de l'émotion nous est cependant apparue insuffisamment caractérisée en ce qui concerne les processus de groupement. Or dans la schizophrénie, les processus perceptifs sont altérés précisément quand il s'agit d'organiser l'information. Nous nous sommes interrogés sur la façon dont les facteurs émotionnels interagissent avec les processus de groupement visuels et quelles sont les conséquences éventuelles sur la façon dont les informations visuelles sont organisées et explorées.

Cette problématique n'a pas encore été étudiée, et notre travail a consisté à développer un nouveau paradigme pour l'explorer. A ces fins, nous avons construit et testé 16 paradigmes consécutifs. Nous nous sommes basés sur un paradigme proposé par Beck et Palmer (2002) qui permet de révéler les processus de groupement en vision. Nous avons ajouté différents stimuli émotionnels aux figures habituelles pour en tester l'influence sur le groupement. Les différentes épreuves successives que nous avons mises en place nous ont permis d'affiner le paradigme et de contrôler les différents facteurs susceptibles de biaiser les données (exemples fig. 2).

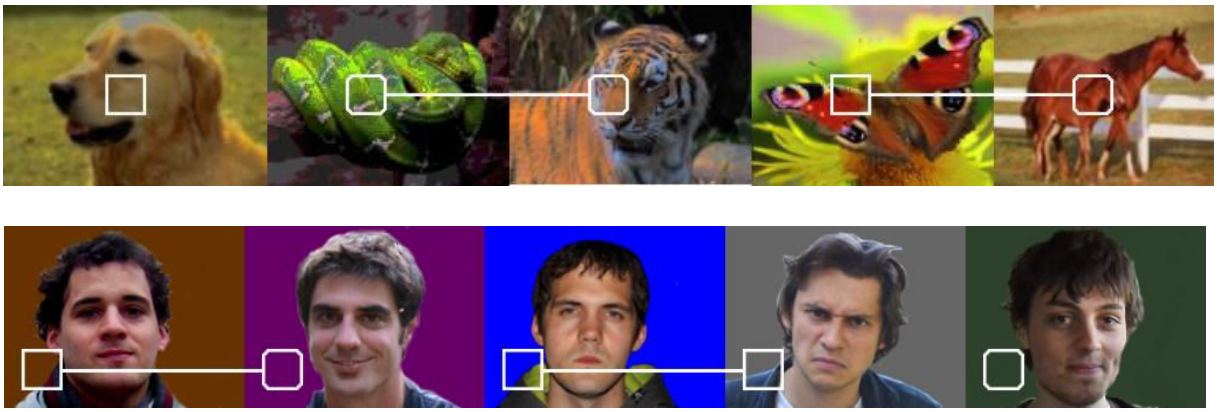

Figure 2. Exemples des paradigmes conçus pour étudier l'influence des stimuli émotionnels sur le groupement. Les 5 figures (carrées avec des angles droits et carrées avec des angles émoussés) représentent les stimuli nécessaires pour effectuer la tâche. Les images au deuxième plan ne sont pas pertinentes pour la tâche et sont des distracteurs. La tâche était de détecter la paire de formes adjacentes et identiques et d'en déterminer la forme. Cette paire de figures cibles était située sur deux images de valence opposée (l'une positive et l'autre négative, condition non congruente), deux images négatives ou deux images positives.

Les résultats obtenus chez les sujets sains suggèrent que les photographies de visages véhiculant une émotion positive et celles d'animaux véhiculant des émotions négatives interfèrent pendant l'organisation perceptive de l'environnement. En présence de telles images, leur saillance prend le pas sur des processus de groupement pourtant réputés automatiques. Les résultats montrent que les différentes émotions peuvent affecter la manière dont nous explorons l'environnement et entrer en compétition avec l'organisation dérivée des processus de groupement.

Le paradigme pouvait dès lors être utilisé pour étudier ce fonctionnement chez les patients schizophrènes, lesquels présentent des symptômes qui touchent à l'expression émotionnelle, ainsi que des troubles de la perception. Est-ce que leur perception différente est liée à un affect émoussé ou à d'autres problèmes touchant les émotions? Ou est-ce que l'altération de la perception déforme la perception de l'émotion? Nous présenterons dans la thèse les résultats d'une première étude utilisant notre paradigme chez les patients schizophrènes. Les résultats ne montrent pas de différence significative entre les patients et les sujets sains appariés, suggérant une interférence normale entre les facteurs émotionnels et les processus de groupement (fig.3). Par contre nous n'avons utilisé que des visages pour véhiculer des émotions, et l'étape ultérieure sera de tester les effets avec un autre paradigme.

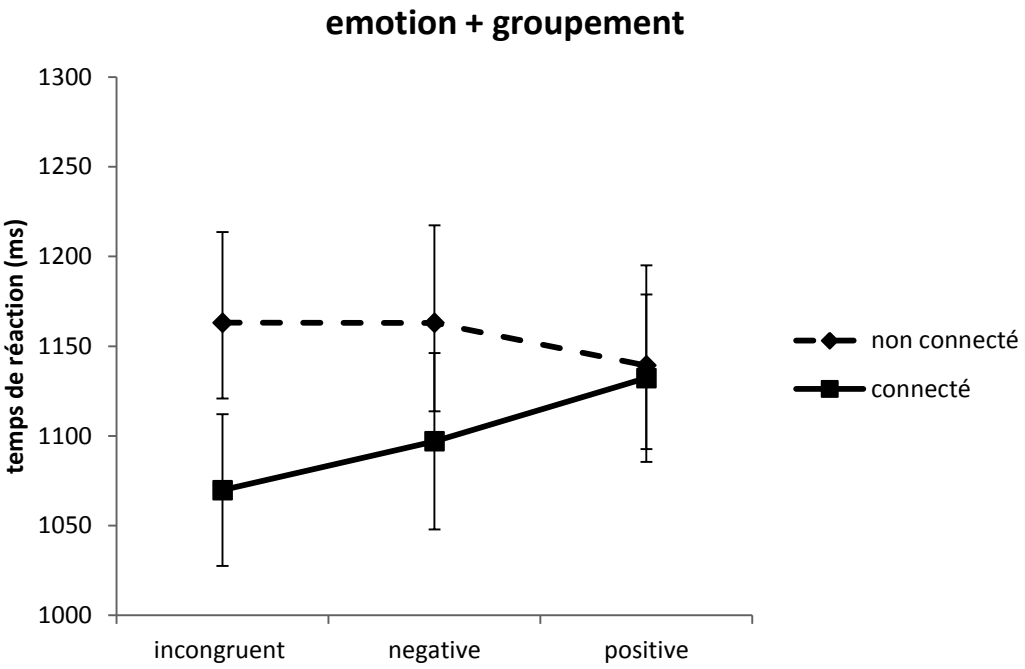

Figure 3. Illustration de l'interférence d'images avec des valences émotionnelles sur les effets du groupement (avec de gauche à droite, les conditions dans lesquelles les cibles sont localisées sur deux images de valence différente, deux images négatives, ou deux images positives). Les résultats sont moyennés sur les groupes de patients et de contrôles, en l'absence de différence entre les groupes. Les résultats montrent que l'avantage apporté par la présence de connecteurs est annulé quand les images distractrices au second plan sont des visages positifs.

Etude 2

Notre deuxième approche vise à éclaircir les troubles de la perception de la douleur chez les patients schizophrènes. Chez les patients, une insensibilité à la douleur a souvent été soupçonnée au regard de nombreux cas d'automutilations, de retards à la médicalisation et des problèmes de santé majeurs, urgences abdominales ou infarctus notamment. Ceci semble être indépendant du traitement par neuroleptiques. Malgré ses répercussions invalidantes, ce trouble a été peu étudié. Or des descriptions similaires ont été rapportées concernant la perception de l'émotion, qui a été décrite comme diminuée chez les patients. Cependant plusieurs études ont suggéré une perception préservée de l'émotion, même si

son expression est altérée. Ces études remettent en question la notion selon laquelle les patients sont insensibles aux stimulations de l'environnement, et nous avons appliqué cette question à la douleur. Nous avons voulu vérifier si des patients stabilisés, chroniques présentaient effectivement une insensibilité à la douleur, et dans quelle mesure les troubles observés étaient liés à un problème d'expression ou de sensation de la douleur, à l'attention ou à l'émotion. Pour répondre à ces questions, nous avons distingué les réponses objectives (EEG) et subjectives (verbales) à une stimulation électrique ou une image chargée émotionnellement (réponse du sujet qui évalue sa douleur ou son émotion sur une échelle visuelle analogique).

Nous avons inclus 21 patients et 21 témoins dans cette étude. Nous avons comparé leur perception de la douleur et exploré les dysfonctionnements attentionnels, émotionnels et cognitifs qui pourraient sous-tendre les troubles de la sensibilité à la douleur.

Les résultats de cette étude suggèrent que les patients ne sont pas insensibles à la douleur ou aux images négatives et neutres. L'enregistrement EEG montre même une réponse excessive et très précoce à ces stimulations. En effet, les potentiels évoqués observés dès 50 ms après les stimulations sont plus élevés chez les patients par rapport aux sujets contrôles (fig.4). Cela indique une hypersensibilité des patients à un niveau de traitement très précoce de l'information. Les altérations cognitives et la littérature dans la schizophrénie nous ont amenés à proposer une interprétation en termes de défaut d'anticipation et de filtrage de l'information douloureuse et émotionnelle.

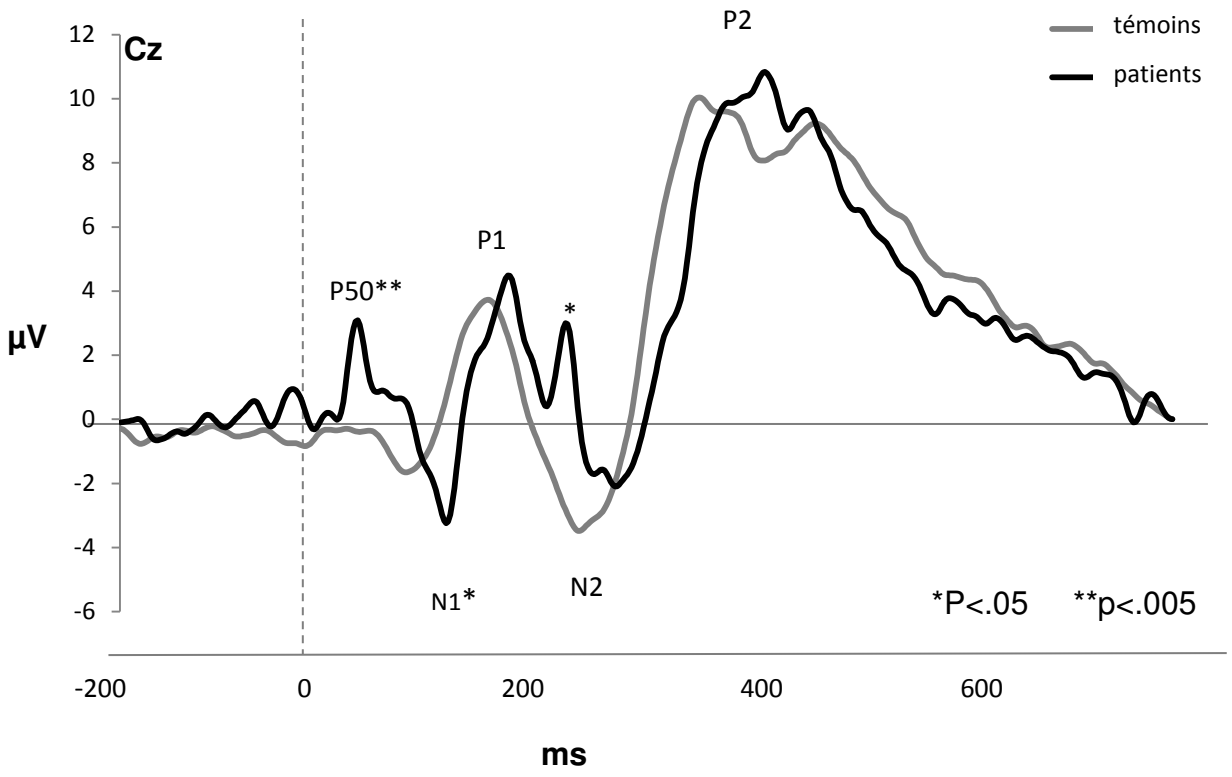

Figure 4. Courbe moyennée des potentiels évoqués après les stimulations électriques à 1800µA. Les résultats montrent des différences entre patients (gris) et témoins (noir). Les patients présentent des potentiels évoqués précoces plus larges que les témoins.

Chacune des deux études nous a permis, de différentes manières, d'aborder la question de l'émotion, et de ses effets sur la perception.

Dans notre première étude nous avons élaboré un paradigme nous permettant de mesurer l'influence de différentes émotions sur la façon dont nous organisons et explorons notre environnement visuel. Ce paradigme nous permettra de vérifier dans quelle mesure les altérations de l'affect chez les patients rendent compte de leurs difficultés à explorer leur environnement de manière organisée et cohérente, ou si au contraire les influences de l'émotion sont préservées.

La deuxième étude a mis en évidence une hypersensibilité dans le traitement précoce de la douleur chez les patients schizophrènes. Les patients ne sont pas seulement sensibles aux stimulations électriques mais également à des stimuli émotionnels négatifs. Ces résultats peuvent faire moduler la prise en charge des patients lors d'une anesthésie, mais nous incitent aussi à reconsidérer notre compréhension des patients eux-mêmes, trop souvent perçus comme imperméables à leur environnement.

L'ensemble de nos travaux ont exploré des aspects importants de la cognition dite chaude (parce qu'elle prend en compte les réponses émotionnelles). Nous avons pu mettre en évidence une hypersensibilité chez les patients qui contredit des idées préconçues et soulève un certain nombre de questions. A quel point est-ce que ces différences affectent l'adaptation des patients à leur environnement ? Quelle importance ont les mécanismes précoces et tardifs ? Comment est-ce que les troubles précoces du traitement de l'émotion affectent l'organisation de l'environnement ? Est-ce que les symptômes lié à l'émotion relèvent de cette différence ou est ce qu'elle en est la cause? Est-ce que l'émoussement de l'affect protège les patients qui présentent des problèmes de filtrage de l'information émotionnelle? Dans cette thèse nous discuterons les différentes réponses possibles à ces questions.

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Part 1

Introduction

Chapter 1: Schizophrenia

1.1. Not what everybody thinks

Schizophrenia - You mean a person with two personalities?

No, this is one of the stigmatizing false beliefs about schizophrenia that exist today showing that schizophrenia is still a mystery to people who are not directly confronted with it. Other and even worse examples of these false beliefs are that schizophrenic patients are dangerous and unpredictable. Thus, people are afraid of them and even though these representations are false, they have been stable and are anchored in a wide range of countries in the world. In most of these countries the word schizophrenia or schizophrenic has even become a contemporary expression and is used as a metaphor to describe illogical actions (Vahabzadeh, Wittenauer, & Carr, 2011). Furthermore various media such as movies and the press contribute to these false beliefs and aggravate them in different ways. In movies with a schizophrenic main character for example, the sick character is usually represented as dangerous or criminal and often commits homicide (Owen, 2012). In newspapers on the other hand, real life events are selected according to the attraction that articles can provoke, which is exalted when a person with schizophrenia has committed the crime (Stuart, 2006).

Hence it is more likely to read about a person suffering from schizophrenia who has committed a crime, than about one being the victim of a crime. But in fact it has been shown that their risk to be the victim is 6 times higher than for the general population (Teplin, McClelland, Abram, & Weiner, 2005). On top of that, the percentage of suicide in patients is a lot higher than in the 'normal population' which highlights that they are rather dangerous for themselves than for others (Limosin, Loze, Philippe, Casadebaig, & Rouillon, 2007).

The reason why these representations persist, could be linked to different clinical features observed in schizophrenic patients: for example their lack of emotional expression (the blunted affect) might make people feel uncomfortable around them and maybe even threatened. Another explanation could be a misunderstanding of the clinical symptom 'dissociation'. It could be understood as a dissociation of personalities though this is not the case. When psychiatrists speak of the symptom dissociation in schizophrenia, they are talking about the dissociation of different features as for example emotional and verbal expression.

All these misconceptions of patients with schizophrenia show that there is still a lot of work that has to be done in order to rectify the representation of this mental illness. In order to do so, it is important to understand schizophrenia with all its facets.

The approach we chose to enlarge the knowledge of schizophrenia, is to study patients' perception in two different fields: pain perception and visual perception, which might both be linked to the blunted affect observed in patients and to cognitive deficits. First, we briefly summarize the clinical and experimental elements issued from the pathology that led to our questions. Then we will expose the basic knowledge issued from the field of cognitive neuroscience that we needed to perform our studies, with a focus on the interaction between cognition and emotion. We detail specific knowledge associated to pain perception and visual perception in separate chapters, before the description of our studies.

1.2. A multifaceted mental disease

False beliefs about schizophrenia show that this mental illness is yet largely misunderstood; however we cannot only blame the media for this false image of schizophrenia. It is important to clarify that schizophrenia is a very severe and handicapping mental illness, which affects about 1 % of the population, and whose definition and diagnoses have, and probably will still change over time. In addition the diagnosis cannot be approved by a physical exam as it is possible for other diseases such as diabetes or cancer. All in all the concept of schizophrenia lacks clarity and certainty.

The observation of schizophrenia symptoms and the attempt to assemble these symptoms into one concept has been a subject of research for decades. Schizophrenia has first been described by Bleuler (Bleuler, 1934) and Kraepelin (Kraepelin, 1919), two psychiatrists recognized as the founders of modern psychiatry. Kraepelin observed and conceptualized a broad range of psychoses, and classified one group of psychosis (e.g. hebephrenia, paranoia, catatonia) under the name dementia praecox. This classification was almost merely based on the evolution and outcome of these disorders, for dementia praecox meant a deterioration of the patient's state and only a rare possibility of recovery (Burns, 2007). Due to a general deterioration, the patient would progressively neglect basic needs like eating and drinking which eventually led to death. The name dementia praecox was changed later on by Bleuler, who did not consider dementia as one of the prevalent symptoms. He named the concept schizophrenia and classified its symptoms into the 'fundamental' symptoms which he thought were directly caused by the impairment of biological processes, i.e. the 4 A's: **a**ffect (flat or inappropriate), loosening of **a**ssociations,

autism, and **a**mbivalence, and the 'accessory' symptoms which were not directly linked to biological processes, e.g. delusions, hallucinations and cognitive deficits (Bleuler, 1934; Moskowitz & Heim, 2011; Noll, 2009).

Today schizophrenia is considered as one of the most frequent chronic psychoses. Its diagnosis is still exclusively based on clinical interviews with a psychiatrist. The different symptoms are defined in the DSM-IV (American psychiatric association, Crocq & Guelfi, 2004). Recently a new edition of DSM was published, the DSM V. In this new edition, different details have changed, but the definition of schizophrenia has remained largely the same. Since our study started in the year 2010, the definition of schizophrenia is based on the DSM-IV (table 1). Symptoms are classified in positive and negative symptoms as well as the presence of a 'disorganization'. Positive symptoms are defined as an excess or distortion of a normal function which are additions to normal thoughts, emotions or behaviors, as for example: delusions and hallucinations. Negative symptoms represent the 'deficit symptoms' such as e.g. anhedonia, flattening of affect and reduced social activity. The symptoms that are related to disorganization can occur in different forms: they can affect the speech (word salad), actions and thoughts, but can also affect the clinical symptoms which may result in a disorganized hallucination for example.

The diagnosis does not involve any biological evaluation, but fundamental research studies and biological exams of patients have led to supplementary knowledge about this disease. Today we know that there are alterations at the neurobiological levels. For example, and to cite only the best known abnormalities, patients seem to produce more dopamine

than healthy control subjects especially during the acute phases[1] of the disease (Baumeister & Francis, 2002), and the size of patients ventricles has been shown to be enlarged (Stevens, 1997). Unfortunately it is not possible to diagnose schizophrenia on the basis of these characteristics yet, since the dimension of these neurobiological alterations, differ from individual to individual. However, it is possible to link some of the clinical features to the neurobiological alterations. For example, the excess of dopamine has been correlated to positive symptoms during the acute phase of the disease (Davis, Kahn, Ko, & Davidson, 1991).

In addition to neurobiological alterations, the existence of cognitive impairments is now well admitted. These impairments, and especially those affecting perception or attention, have often been correlated with negative symptoms as well as the disorganization (Brébion et al., 2014; Horton & Silverstein, 2011; Schenkel, Spaulding, & Silverstein, 2005). Besides, these impairments can deteriorate the patients' quality of life, possibly because they affect their capacity to integrate information and to be independent in our social world (Bobes, Garcia-Portilla, Bascaran, Saiz, & Bouzono, 2007). Today the cognitive impairments in attention (Luck, Ford, Sarter, & Lustig, 2012; Luck & Gold, 2008; Nuechterlein, Luck, Lustig, & Sarter, 2009) and memory (Gur & Gur, 2013; Wolf, Vasic, & Walter, 2006) have been largely studied. Different techniques have been developed in order to improve patients performances and capacities. For example 'remediation techniques' which have been shown to improve autobiographical memory which paves the way for the elaboration of remediation techniques that could help patients in their everyday life (Potheegadoo, Cordier, Berna, & Danion, 2014).

[1] The course of schizophrenia is often divided into different stages in which the acute phase corresponds to the one in which the symptoms are most pronounced.

However there are other cognitive impairments which are also likely to affect patients' quality of life, such as emotion perception and perception in general. In order to adapt to the environment we have to perceive the different stimuli that surround us, as well as ourselves. Therefore visual perception as well as proprioception, somatosensation and pain perception are important. We have to be able to evaluate the different stimuli in order to react in the best way. A giant bear should make us flee and we should seek nutrition when we are hungry. The perception of social cues and their interpretation necessitate an intact emotion perception which will enable us to interact with others, make friends or seek help. Here we will examine visual as well as pain perception in order to get a better understanding of how they are affected by emotion and whether this interaction between emotion and perception is linked to impairments seen in schizophrenia.

Diagnostic criteria for Schizophrenia

A. *Characteristic symptoms:* Two (or more) for the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (for example frequent derailment or incoherence)
4. grossly disorganized or catatonic behavior
5. negative symptoms, that is,, affective flattening, alogia, or avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. *Duration:* Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (that is, active-phase symptoms) and may include prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (for example, odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and Mood Disorder exclusion:* Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion:* The disturbance is not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition.

F. *Relationship to a Pervasive Developmental Disorder:* If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are present for at least a month (or less if successfully treated).

Table 1. Excerpt from the DSM IV American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, pp. 285–6.

1.3. Cognition and emotion in schizophrenia

1.3.1. Cognition

Attention deficits in patients with schizophrenia have already been described by Kraepelin and Bleuler. Today, thanks to the emergence of the concept of cognition, and to the enlargement of our means to measure and evaluate deficits with neuropsychological tests, imagery and psycho-experimental paradigms, several deficits in cognition have been assessed and well defined: deterioration of vigilance and attention over time, difficulties in memorizing verbal as well as visual information, impairment of reasoning, problem solving, working memory capacities as well as difficulties in recognizing facial affect and social cues (Keefe & Harvey, 2012). However these impairments do not occur systematically in patients with schizophrenia, thus they cannot be generalized and considered as a symptom. Furthermore, the severity of these impairments differs between individuals.

As we can see, pain or visual perception, are not at the forefront of the cognitive deficits, but may nonetheless affect the conscious experience of patients. This possibility is suggested by the patients' personal reports. They have difficulties to detail their experiences in a coherent way, thus their verbal reports have to be taken with caution. Yet, psychiatrists have collected a range of verbal reports that give some insight on the patients' inner experiences. In relation to distortions of the visual perception and dissociation experiences that patients can suffer from, we have chosen two quotations, in which patients describe how difficult it can be for them to make sense of the environment.

Patient 1: "Things go too quick for my mind. Everything is too fast and too big for me –too quick to study. Things get blurred and it's like being blind. I can't make them out clearly.

It's as if you were seeing one picture one minute and another picture the next. I just stop and watch my feet. If I move, everything alters every minute and I have no control over my legs. My legs are too quick for the top half of my body - it's my head that's weak. I followed the sun and it seemed to drive me along. The sun seemed too big for me and it was coming closer. Everything else seemed to be coming closer and bigger all the time. I tried to make the air turn back. It was frightening. That was a long time ago - last year.

Patient 2: Everything I see is split up. It's like a photograph that's torn in bits and put together again. If somebody moves or speaks, everything I see disappears quickly and I have to put it together again." (Chapman, 1966).

One difficulty here is to understand which cognitive deficits account for the patients' difficulties and how they interact. More generally, different cognitive deficits can have a severe impact on the quality of life of the patient. A deficit in attention, memory and processing speed can make it impossible to keep a job or even take part in and/or follow a conversation. But whatever the explanation for the patients' complaints, the quotations cited above highlight in which way the quality of life is deteriorated. Moreover the social life is at stake, which can be aggravated by a lack of perception of social cues. It is therefore very important to treat and understand cognitive disorders in order to improve the quality of life for the concerned individuals.

Taking into account the importance of emotion and perception in our everyday life as well as my personal interest for these processes, we have built our two distinct paradigms. For these paradigms we chose two perceptual mechanisms which have been shown to be impaired in schizophrenia, i.e. visual perception and pain perception, and we investigated

the impact of emotion in these processes. Impaired emotion perception has been described in patients which seems to be closely linked to the clinical symptom blunted affect.

We will briefly describe the clinical importance of blunted affect in order to introduce the purpose and the outline of the two studies we conducted.

1.3.2. Emotion/ Blunted affect

The blunted affect is evaluated by the observation of an unchanging facial expression, decreased spontaneous movements, paucity of expressive gestures, poor eye contact, affective non responsiveness, inappropriate affect, and lack of vocal inflections (SANS Andreasen 1982, 1984; affective flattening subscale items). The first psychiatrists who described a disturbance of the emotional functioning in patients were Bleuler and Kraeplin in 1940. They described the symptom as blunted affect and hypothesized that the patients were nevertheless able to experience these emotions. They suggested that the symptom was a consequence of a lack of expression. A few years later Rado (1953) suggested a different possibility: He thought that it wasn't just a lack of emotional expression but rather a complete anhedonia of positive emotions, meaning patients do not experience these emotions at all.

Until recently this last conception has been held to be true. However today it has been shown that patients rate the emotional stimuli in the same way as healthy controls. They also rate their own feelings similarly in emotional situations (Kring, Kerr, Smith, & Neale, 1993; Kring & Caponigro, 2010), and even show comparable physiological responses such as skin conductance or startle modulation. However they are outwardly less expressive

than healthy subjects (Kring & Moran, 2008), which partly explains the clinical observations. The lack of expression is also supported by experimental evidence: in comparison to control subjects emotions are less visible on the patients faces (Berenbaum & Oltmanns, 1992). These studies suggest that emotional disturbances are a matter of expression, as already proposed by Bleuler and Kraeplin in 1940.

This conclusion may still not be definitive, though. Brain imaging studies have investigated whether brain activation during emotion processing differs in patients and controls. Studies have evaluated the reaction to different kinds of emotion stimuli, and contrasting results range from testifying an enhanced activation, to the observation of a decreased activation in certain regions such as the amygdala (Aleman & Kahn, 2005). These discrepancies still reflect that there are some differences in the processing of emotional stimuli. Kring & Caponigro (2010) hypothesize that there might be differences in the processing of these stimuli in patients which is difficult to evidence behaviorally.

Independent of the debate on emotion processing, blunted affect is one of the only symptoms which does not seem to fluctuate over time. In addition, patients who suffer the most from blunted affect are also those with the largest difficulties in social functioning (Evensen et al., 2012). This is mainly due to the importance of emotion expression and comprehension during social interactions, but blunted affect might also be related to other perception processes. Here we will try to shed light on a possible relationship between emotion processing and visual as well as pain perception, two mechanisms which have been shown to be affected in patients with schizophrenia.

1.4. Deficits in visual and pain perception in patients with schizophrenia

1.4.1. Pain perception

When Bleuler and Kraeplin first started to describe and define the mental illness schizophrenia, they observed patients who were less sensitive to pain or even completely analgesic. Even though different characteristics and the way to classify and diagnose schizophrenia have changed over time, today psychiatrists still worry about their patients' insensitivity to pain. The clinical observations are varied, which is probably why the difference in pain perception has never been considered as a symptom on its own. Some patients present a lack of complaint when they are in physical pain, which has sometimes resulted in severe consequences such as an acute abdomen or the amputation of an inflamed member. Multiple case studies report spectacular cases which highlight the severity of this problem (Agorastos, Huber, Dunker, & Wiedemann, 2011; Murakami et al., 2010; Retamero & Paglia, 2012). Other consequences are severe auto mutilations. Patients either inflict mutilations upon themselves or do not pay attention or react when they for example burn their fingers or lips with the end of a cigarette.

The clinical observations usually regard patients who are in an acute phase (when describing auto-mutilations), however it is unknown whether pain perception alterations also occur during the chronic phase. Are all patients, in every stage of the illness, insensitive to pain? As the case reports vary in intensity and circumstances, and as experimental evidence is scarce, it is difficult to know when and how patients feel pain.

With regard to the symptoms, disturbances in pain sensitivity could be linked to different characteristics of schizophrenia, such as the blunted affect, dissociation or

cognitive deficits. However, the first questions that need to be answered are, whether patients are really insensitive to pain and whether it is a matter of perception or expression. Do patients with schizophrenia fail to feel the pain, or do they feel it but do not express it outwardly? If there is a disturbance in sensory processing, could this be linked to an excessive production of dopamine or a different biochemical alteration that can be seen in schizophrenia? Finding answers to these questions might make it easier to treat patients when they are physically ill and thus improve their quality of life. Another important aspect is anesthesia in surgery. In order to give patients the right amount of anesthetics, anesthetists have to know whether the patients pain processing is intact or not and in which way it is altered in order to adapt the doses of anesthetics.

1.4.2. Visual Perception

Visual perception in schizophrenia has been described to be disrupted by patients themselves, and this disruption can be very handicapping. We have already presented two examples in the anterior section; however we will present a third one which describes in a good way the fragmentation of the stimuli, experienced by the patients.

Patient 3 "Everything is alright when I stop. If I move everything I see keeps changing, everything I'm looking at gets broken up and I stop to put it together again." (Chapman, 1966).

These different quotations show that the visual fragmentation can have different dimensions. Some patients have difficulties assembling the different objects of the environment, which serves to create a meaningful visual environment, whereas others have difficulties even for perceiving one object as a whole.

However, visual disturbances are not the most frequent and spontaneous complaints of the patients. Hence these difficulties have not been listed as a symptom on its own. It can be related to different other symptoms and difficulties, though, such as fragmentation of thought and action or attentional deficits (Silverstein & Keane, 2011).

In any case this disruption in visual perception makes it difficult for patients to perceive the world as a whole, and might even alter what they see.

Altogether, cognitive, emotional and perceptual deficits make life harder for schizophrenic patients as they reduce their quality of life and make social integration even harder than it already is. The lack of emotional expression on their faces makes it hard for them to communicate. Insensitivity to pain can be dangerous and has severe medical consequences. Finally cognitive deficits exclude them from most of the working possibilities.

Thus it is important to study and understand where these symptoms come from and to find a way to treat them. In the next chapter we will introduce the interaction between cognition and emotion in general which will help to understand the importance of these interactions and the possible impairments in patients.

Chapter 2: General aspects of cognition and emotion

2.1. Cognition

Cognition is a very vast concept which has different definitions depending on the discipline. In disciplines such as cognitive neuroscience, cognition is the umbrella term for mental activity which encloses perception, action, emotion, motivation, language, learning and memory (Kandel, Schwartz, & Jessell, 2000). Each one of these concepts can be subdivided into multiple functions, for example perception encloses visual, olfactory, touch, somatosensory, auditory and gustative perception. Action on the other hand comprises movement of the body, talking, thinking, playing and any other behavior that can be initiated by a human being.

Studying the brain and cognition over centuries has made it possible to assign different functions to specific brain areas. It is generally acknowledged that planning and cognitive control is attributed to the frontal lobe of the brain, visual information is processed in the occipital lobe and the temporal lobe contains auditory, visual and multimodal processing areas. The parietal lobe on the other hand receives sensory input about touch, pain, temperature and limb position, and is involved in coding space and coordinating actions (Gazzaniga, Ivry, & Mangun, 2009).

However, already in these few examples, we can notice some overlapping, which indicates that this is not yet the whole story. Early studies on visual perception have shown that the image that we perceive is actually projected the other way around on the back of the eye, which added another dimension to research and the understanding of cognition (Baars, 2010) which is representation. Representations are not unique to visual perception but are an important part of any other kind of cognition. Other examples are language and reading. In order to understand the words, we need a representation of what the word means. Thus over time we accumulate knowledge which helps us to understand, perceive

and act the right way. The functional framework elaborated by Baars and Gage (2010) sums up the interplay between the different players very well (fig.1).

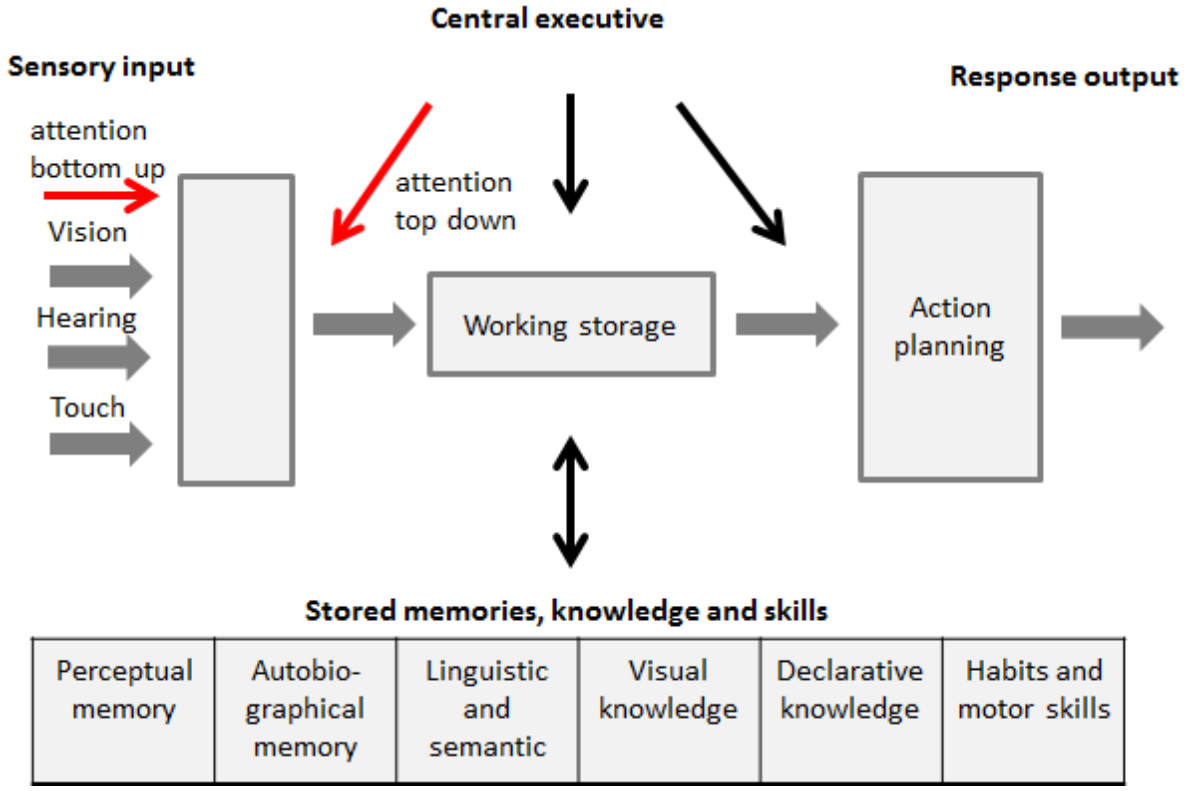


Figure 1. Model of cognition, adapted from Baars and Gage (2010)

Nevertheless there is one important factor missing which has for a long time not been considered in cognitive processing, or if mentioned, it was mentioned as a process well apart. This aspect is emotion, which is today more and more considered as a key player in cognition since it seems to be implicated in almost every aspect of cognition. In the domain of social cognition and cognitive psychology for example, the definition of cognition refers to what the individual perceives in a particular context with the aim to integrate, adapt, or just understand social mechanisms (Lemaire, 2006). Briefly, social mechanisms denote the actions of a human being as well as the interactions with other human beings which are influenced by the personal characteristics. These are unique for each individual (desires,

beliefs and opportunities) and will produce a particular outcome (Hedström, 2005). These interactions can range from a simple one on one conversation to more complex interactions that involve more than two people. One individual can for example have a great effect on a group (leader), and a group can have a great impact on an individual (peer pressure). These interactions and influences can be positive or negative and will have different impacts on the individual depending on his or her own nature. Regardless of these specific examples, all these actions and interactions are in some way, based on, or linked to, emotions. Hence in order to interact with others in the most adapted manner, we have to be able to understand the others emotions, as well as our own emotions in order to adapt our behavior and actions.

2.2. Emotion

As depicted in the model of cognition above, emotion was not always considered as an important part of cognition, and the interaction between emotion and cognition was not recognized. The first scientists interested in emotion were philosophers such as René Descartes and David Hume (Damasio, 2004). Later on Charles Darwin integrated emotions in his theory of evolution: he attributed to emotion the purpose of assuring communication and survival (Darwin, 2007). Today emotions are still studied from different perspectives comprising amongst others psychology, psychiatry and sociology. Furthermore they have become of great interest for neuroscience since the late 20th century (Lane & Nadel, 2002; Panksepp, 1998).

Consequently the concept of emotion has changed over the years. Perspectives have been enriched, and the development of new techniques has allowed us to better understand

emotion, and to visualize and follow the activity in the brain that accompanies conscious or unconscious emotional experiences.

But let us start at the beginning. Emotions are subjective experiences which assign a certain value to the situations and stimuli of our daily lives and are of great importance for human relationships (Dolan, 2002). In a very simplified way, emotion is generated by the interaction of physiological, cognitive, and psychological components. Physiological components represent the bodily changes such as the raise of the heart rate, sweating and the down regulation of other mechanisms such as digestion, which are triggered by the emotional stimuli and are automatic reactions. The cognitive and psychological components interact in order to attribute a certain meaning to the stimulus, by means of memory, evaluation and reevaluation of the situation. Hence they guide the interpretation of the stimulus which is necessary to adapt the response (Dolan, 2002).

In terms of neuroscience, a first automatic reaction triggers physical responses of the autonomic nervous system (such as the increase of the heart rate) which is guided by the brainstem and the amygdala. Once these mechanisms have been activated, the cerebral cortex comes into play and allows us to evaluate the situation on a conscious level and maybe readapt our behavior. There are different situations which illustrate this process. For example: when a person is concentrated on something and does not notice the approaching colleague, the concentrated person might startle when he suddenly perceives a motion right next to him. There is no possible way to control this reaction, however once the time has allowed the individual to realize that it is just a colleague, it is possible to reevaluate the situation consciously and to realize that there is no need to fight or flee. Thus the body can calm down again. In a different circumstance, for example when the automatic reaction is

caused by a dangerous snake, it might be crucial that the body is ready before the time consuming cognitive reevaluation. This time difference between the first unconscious and the second conscious evaluation of the stimuli is consubstantial with a conceptual differentiation between two dimensions of the emotional stimuli. The first dimension corresponds to the quick evaluation and is called arousal: it can range between totally calm and very excited. The second dimension corresponds to the valence of the emotion which ranges between positive and negative.

Up to today no uniform model of emotion has been accepted yet. The existing models of emotional functioning differ mainly in two aspects: The definition of emotion categories (What is considered as an emotion?) and the relative involvement of physiological reactions, attention and cognition in the experience of emotion (Moors, 2009). These two questions have not been completely resolved yet and I will briefly describe the hypotheses that have been developed to answer them.

First, what is an emotion, and what is not? Paul Ekman defined six basic emotions that were all defined by a facial expression and a physiological response which are common for everybody: anger, surprise, disgust, fear, happiness and sadness. Later on, he broadened his definition and added other emotions as for example amusement, contempt, and embarrassment (Ekman, 1999). His point of view has been criticized and others have added complementary emotions such as displayed in table 2 (Parrott, 2001). These complementary emotions include for example jealousy. According to Ekman however, jealousy is not an emotion because it comprises motivation and has no unique pattern (jealousy can make you sad or angry) (Sabini & Silver, 2005). Today it seems as if the six basic emotions proposed by

Ekman have been widely accepted, however whether to include emotions such as jealousy is still discussed and raises discordances.

Primary emotion	Secondary emotion	Tertiary emotion
love	affection	adoration, affection, love, fondness, liking, attraction, caring, tenderness…
	lust	arousal, desire, lust, passion, infatuation
	longing	longing
joy	cheerfulness	amusement, bliss, cheerfulness, gaiety, glee, jolliness, joy, delight…
	zest	enthusiasm, zeal, zest, excitement, thrill, exhilaration
	contentment	contentment, pleasure
	pride	pride, triumph
	optimism	eagerness, hope, optimism
	enthrallment	enthrallment, rapture
	relief	relief
surprise	surprise	amazement, surprise, astonishment
anger	irritation	aggravation, irritation, agitation, annoyance, grouchiness, grumpiness
	exasperation	exasperation, frustration
	rage	anger, rage, outrage, fury, wrath, hostility, ferocity, bitterness, hate
	disgust	disgust, revulsion, contempt
	envy	envy, jealousy
	torment	torment
sadness	suffering	agony, suffering, hurt, anguish
	sadness	depression, despair, hopelessness, gloom, glumness, sadness…
	disappointment	dismay, disappointment, displeasure
	shame	guilt, shame, regret, remorse
	neglect	alienation, isolation, neglect, loneliness, rejection, homesickness, defeat
	sympathy	pity, sympathy
fear	horror	alarm, shock, fear, fright, horror, terror, panic, hysteria, mortification
	nervousness	anxiety, nervousness, tenseness, uneasiness, apprehension, worry…

Table 2. Table of emotions classified by Parrott (2001).

The second discordance concerns the mechanisms subtending emotion. Until the late nineteenth century, emotion was thought to be produced after the cognitive interpretation and evaluation of the scene or situation. More precisely, it was proposed that the situation had to be recognized first. This recognition triggers the conscious emotional responses, e.g. fear, which in turn triggers the physiological responses, such as e.g. a racing heart.

James and Lange revoked this point of view in 1984 and proposed a new opposing theory which was then further developed by Magda Arnold, Stanley Schachter, Joseph Ledoux resulting in the 'appraisal theory'. According to these authors, the situation is evaluated in different steps. The first step occurs on an unconscious implicit level. It is then followed by bodily changes and action tendencies[2] and finally by the conscious experience (in Kandel et al., 2000). This process implies that the final experience of emotion is not a single and spontaneous reaction but rather a construction. However in this model, the appraisal i.e. the cognitive evaluation and conscious understanding of the emotion, is described as predetermined. This means that each emotion has its own pattern of activation that will lead to the conscious feeling of the respective specific emotion (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012).

More recently however, this question has gained more subtleties and has become rather complex. Appraisal theories have added a motivational factor which is followed by physiological responses, whereas network theories do not prioritize a specific order and yet another theory debates whether cognitive and physiological factors arise at the same time and influence each other mutually (Houwer & Hermans, 2010).

[2] what the subject is physiologically and cognitively primed to do (Lowe & Ziemke, 2011)

Regardless of the exact sequence, emotion plays a big role in our lives and influences our actions in multiple ways. For example, the physiological mechanisms that correspond to fear, serve the purpose of gathering as much energy as possible for the fight or flight response. This purpose is still mostly correlated to ancient situations in which human beings had to react very quickly as to save their lives. Thus today some of these emotions can be counterproductive, as for example the stress that the body can produce in an unpleasant or uncomfortable situation which is however not dangerous at all. This can lead to consequences as for example a trembling voice, a stomach ache or too much sweating during an important oral presentation or job interview.

This example highlights but does not represent the whole dimension of influences that emotions have on our daily life. Situations in which we feel afraid, happy, surprised or even angry are good and obvious examples of the influence of emotions: we can feel but not always control them. This is obvious in conscious situations, but less understood and studied for situations in which emotion is processed in an incidental way. More recent models of cognition include emotions as a factor that can change the cognitive processing at different levels. Concurrently, emotion is defined with a cognitive component. All in all this line of research suggests an important interaction between emotion and cognition.

The idea that emotion and cognition interact may also have risen thanks to the evolution of our understanding of neural correlates of emotion and cognition. One of the first researchers who has tried to localize the processing of emotion was James Papez. He developed the idea of the circuit of Papez in the limbic brain on the basis of different major structures and their connections, such as the thalamus, hypothalamus and the cingulate gyrus. The understanding of this circuit has evolved a lot over time. Different structures have

been shown to be implicated in specific emotional processes such as the amygdala, which has been linked to fear processing and conditioning (LeDoux, Cicchetti, Xagoraris & Romanski, 1990; Maren, 1996; Penzo, Robert & Li, 2014). However it has been shown to be solicited for other emotional processes as well (e.g. emotional responses to social stimuli) (Phelps & LeDoux, 2005), highlighting the complexity of these mechanisms as well as the challenge to precisely locate their neural substrates. Today the localizationist idea has been abandoned and it seems clear that emotion is processed in many brain areas, making it all the more plausible that it interacts with cognition.

2.3. Interaction of emotion and cognition

Novel imaging techniques have evidenced interactions between emotion and cognition. Emotional stimuli have been shown to alter attention: Ohman, Flykt, and Esteves (2001) have shown that negative stimuli are rapidly picked out among other stimuli. This effect, called the pop out effect, corresponds to a facilitation of visual search. It is usually explained by the fact that the target information includes feature characteristics that stand in contrast to the other stimuli. This effect has been described for several different features (e.g. color, orientation, contrast, motion) and is largely independent of the number of distractor elements in a display (Livingstone & Hubel, 1988; Treisman & Gelade, 1980). The fact that this effect mainly occurs for negative faces is debated (Becker, Anderson, Mortensen, Neufeld, & Neel, 2011), but our main point here is that emotional information has an effect on visual exploration and attention. Furthermore, it has been suggested that different internal emotional states which are not induced by a specific stimulus, can alter the way we perceive the world. A negative mood could narrow ones attention whereas a positive mood

could incite to explore the world more widely (Fredrickson & Branigan, 2005). Otherwise emotion has been shown to interact with numerous cognitive processes such as memory, motivation and perception (Houwer & Hermans, 2010). These interactions have not only been identified on a psycho-experimental level, but also with imaging techniques. The effect of emotional stimuli on visual perception has been shown to enhance cortical activation in the visual cortex (Lang et al., 1998).

Luiz Pessoa even goes one step further. He proposes that mechanisms for emotion and cognition processing do not only interact, but that they belong together, and cannot be separated at all (Pessoa, 2008). Even though this idea essentially remains a theory, different kinds of studies have shown how strongly emotion and cognition interact.

This eminent link between emotion and cognition is also important in respect to mental illnesses such as depression, bipolar syndrome and schizophrenia. Indeed, all these pathologies display cognitive as well as emotional impairments. Until today these impairments have often been studied separately, or, as regards pain, only scarcely. We aimed at filling this gap for a better understanding of the pathophysiology of schizophrenia.

2.4. Emotion and cognition in schizophrenia

Our goal was to shed some light on emotional peculiarities in patients with schizophrenia, which might influence or even provoke some of the clinical symptoms observed in these patients. More specifically we investigated the interaction between emotion and cognition in two distinct studies. We focused on two cognitive mechanisms and more precisely, visual and pain perception. These two studies are very distinct and were established separately. We will thus briefly describe the aim and general subject of the two studies and separate

them afterwards as to introduce the main mechanisms individually and more precisely. The reasons why we were able to treat these two separate subjects in parallel during the last four years were mainly based on the organization of studies with patients (slow recruitment leaving free time to investigate fundamental questions in healthy volunteers) and on personal interest.

Our first study focuses on the interaction between visual perception and emotion during visual grouping. Emotion as well as visual perception can be altered in patients with schizophrenia and a possible interaction is important to explore. Here we focused on the mechanisms of visual grouping since patients report a fragmented perception. The interaction between emotion and visual grouping has not yet been explored, therefore the main part of this study comprises the creation of a paradigm that allows us to measure this interaction. This study delivers insight into the importance of emotional stimuli in our everyday life in respect to the organization of our visual environment.

In the second study we focused on pain perception which contains an emotional component and has often been described to be altered in patients suffering from schizophrenia.

Part 2

first study

Visual perception and emotion

Chapter 1: Introduction

1.1. Visual perception

Visual perception is a far more complex process as what we would imagine. When talking about something that seems unbelievable or even impossible, a common way to convince your conversational partner that it really happened is to say: 'I have seen it with my own eyes'. This expression gives the impression that the eyes are the main part of the visual process. However, the eyes are part of the brain and are only the first stage in the processing of visual perception, which represents not a simple reflection of the world, but a rather meticulous reconstruction of the stimuli that surround us in the outer world. Moreover, this reconstruction can be accelerated and influenced by anterior experiences. Fig 2 represents a very good illustration of the implication of contextual information.

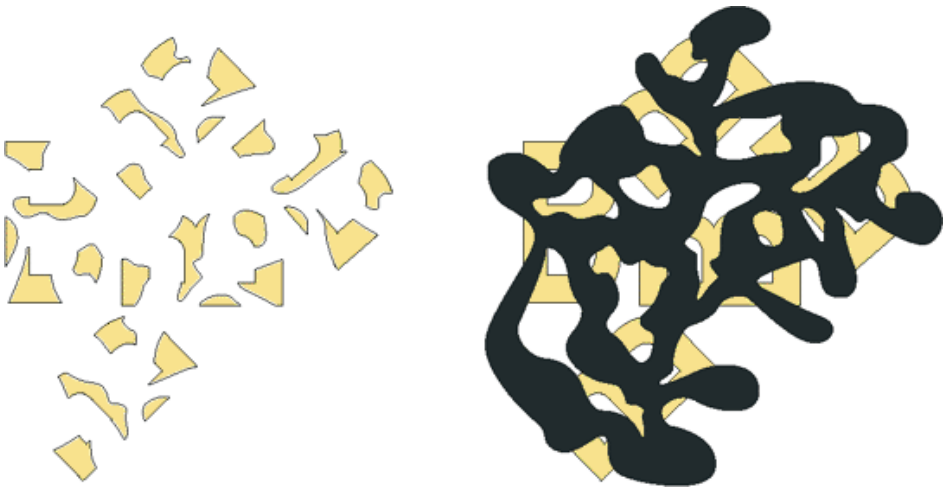


Figure 2. Example of the influence of contextual information in visual perception, taken from Kandel et al. (2000).

So how does this work? I will start at the beginning and try to outline the pathway that creates our visual perception. Visual information is delivered through reflections of light on the objects and our environment. The image is projected on the back layer of the eye, the retina, which is composed of three layers that are involved in the process of

transduction. The first layer contains the photoreceptors, rods and cones, which respond to different wavelengths and transduce the different physiological characteristics into neural stimuli that are transmitted via the optical nerve through the lateral geniculate nucleus in the thalamus to the primary visual cortex.

Up to the primary visual cortex the organization of the information resembles the input on the retina and the different characteristics are processed in parallel pathways. Traditional models of the visual system suggest indeed that local information such as orientation, contrast, spatial frequency and binocularity are analysed locally and in parallel in the primary visual cortex (V1). However this transmission of signals is not enough to allow the recognition of objects. The different characteristics have to be linked in order to create the actual image. Information is believed to pass on from low-order to high-order areas where this information is combined from successively larger parts of the visual field (Vanni et al., 2004). Thus the perceived image is created by a feed-forward process starting with physiological characteristics and resulting in a representation of the environment (Bonnet, 1984). Right at the beginning of the information treatment in retinal ganglion cells, the visual pathways can be separated into two functional different tracks. The dorsal path has been demonstrated to be involved in action. It reaches the parietal cortex and treats complex movements. The ventral path on the other hand, passes through the inferior temporal cortex and is mostly responsible for the treatment of colour and form. It is therefore proposed to be involved in stimulus recognition. The different areas of the visual system seem to be largely interconnected passing on feed-forward as well as feedback information (Lamme, Supèr, & Spekreijse, 1998). Feed forward processing corresponds to what is called bottom-up processing, whereas feedback processing corresponds to top-down processing. For example, there is evidence that the activation of the prefrontal cortex through the dorsal

pathway can alter the on-going feed forward process of the ventral pathway, through top-down pathways (Peyrin et al., 2010). This shows that visual information processing is not a one-way process, but that higher-order areas play a great role in visual perception.

An important part of visual perception is the perceptual grouping. This is the ability to perceive objects as a whole and to attribute every detail that is derived from the unstructured data in retinal images, to the correct form. As already emphasized, primitive information, such as orientation or luminance is first coded locally and in parallel in V1. This information must thus be grouped and segregated correctly in order to derive the form of the objects. Even though this mechanism is not yet entirely understood, several principles have become well established.

1.2. Gestalt laws

Wertheimer (1923) determined that individuals group objects together according to Proximity, Similarity, Closure, Symmetry, Common fate and Continuity (fig.3). Principles of common region, element connectedness and synchrony are also involved (Palmer, Brooks, & Nelson, 2003). The principle of connectedness, for example, means that elements which share a common border or which are physically related tend to be grouped together (fig.3).

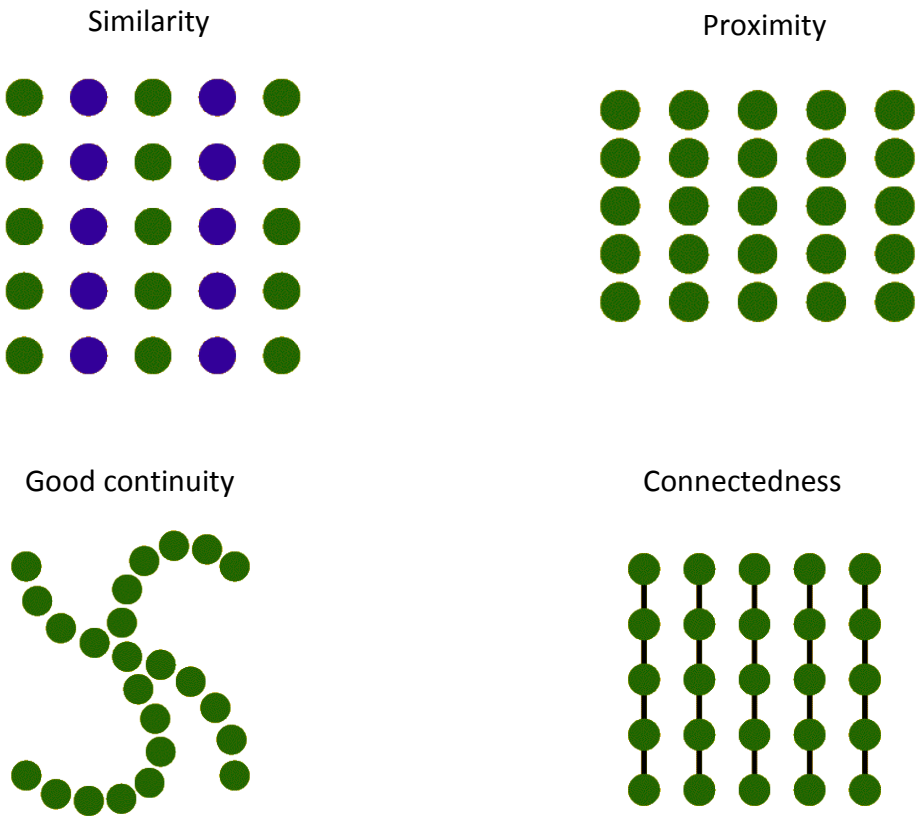


Figure 3. Gestalt laws, examples taken from http://sites.sinauer.com/wolfe3e/chap4/gestaltF.htm

It was first believed that perceptual grouping occurs at a very early stage and that it is unchangeable by later processing. This would mean that grouping occurs in the beginning of visual processing thus in V1 or the secondary visual cortex (V2), and would remain immune to top-down attention processes. Palmer (2002) called this the “early-only view”. However, new findings suggest that grouping is more flexible than previously thought as it has been shown to be modifiable by feedback information from higher order structures. The existence of feedback mechanisms is especially supported by several electrophysiological studies showing an impact of feedback connections on the coding of information in V1 (e.g. Bullier, 2001; Vanni et al., 2004). This indicates a modulation at early stages of visual processing. This modulation might correspond to an amplification of the signal, making each

single item more detectable. This would correspond to a quantitative effect. Furthermore, several experimental psychology studies suggest that grouping itself might be modulated, suggesting, what we call, a qualitative modulation of the signal processing. For example, Beck and Palmer (2002) have asked subjects to find pairs of targets, which were either grouped or not grouped. They have shown that grouping provides an advantage in such a task. Moreover, they have shown that this advantage can be modulated through experimental manipulations. An example for this plasticity is illustrated in figure 4: the features of the central figure can be segregated and then lead to the perception of the number 13, or they are grouped together and lead to the perception of the letter B.

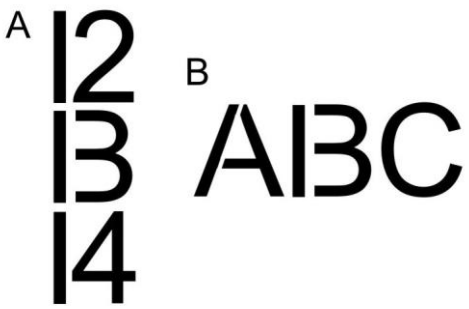


Figure 4. Context can change how we group stimuli together. Here, depending on the context the same stimuli can represent the number 13 or the letter B.

1.3. Visual organization deficits in patients with schizophrenia

By means of experimental paradigms which are based on grouping principles, it has been shown repeatedly that perceptual organization is impaired in patients suffering from schizophrenia (Silverstein & Keane, 2011; Uhlhaas, Phillips, Mitchell, & Silverstein, 2006; van Assche & Giersch, 2011). These impairments have been shown to be specific to schizophrenia as they are intact in patients with bipolar disorder, autism, other psychotic disorders and nonpsychotic mental disorders (Kéri, Kelemen, Benedek, & Janka, 2005; Uhlhaas et al., 2006; Uhlhaas, Phillips, & Silverstein, 2005). Furthermore they have been associated to the disorganization syndrome (Silverstein & Keane, 2011; Uhlhaas et al., 2006).

Giersch and colleagues have shown that visual organization deficits are related to complex top-down regulations (van Assche & Giersch, 2011), and this leads to our question. We have seen that cognition and emotion interact to produce our visual experience. If visual organization deficits in patients are not only the results of impairments at an early processing stage, but also involve complex modulation mechanisms, then this leaves open the possibility that emotion also affects the perception of the patients. Top down mechanisms can indeed be triggered by different kinds of information in the environment. Important examples are emotional stimuli. The detection of emotionally salient information in the environment is important and emotional processing has been suggested to be altered in patients with schizophrenia. This naturally leads us to the question of the interdependency or the influences of emotional processing and perceptual organization. This is all the more important as they might be involved in the emergence of specific symptoms observed in schizophrenia.

1.4. Emotional stimuli – are they all the same?

Before we go into detail on our study, we have to consider the perception of emotional stimuli alone. Our aim here is not to provide an exhaustive review of the vast literature on emotion, since we did not study emotion per se, but its interference with visual grouping. We will thus only briefly summarize some aspects which play a potential role in our results. Basic visual organization is necessary to perceive emotional stimuli. However, as we have described above, emotional information comprise a special function in life and have been shown to facilitate conscious perception (Vuilleumier, 2005). As emphasized, there are several theories that have tried to generalize some of these mechanisms and their consequence as for example the negativity bias, which states that negative, threatening stimuli are processed more rapidly (Mogg et al., 2000).

However, valence is not the only characteristic of emotional stimuli which may play a role in attention attraction. Other characteristics are for example arousal, the singularity of a stimulus (pop out effect) and the type of stimuli. For example faces are special objects that have a particular biological and social significance and might even be associated with some innate or overlearned salience (Domínguez-Borràs, Saj, Armony, & Vuilleumier, 2012; Johnson, 2011). We will focus on faces here, since they play a special role in our experiments. Faces have been of great interest in the past decades and many studies show that they share a special status. Yet findings remain controversial. In particular, two main points are discussed. First it is highly debated whether a bias towards happy or angry faces exists and second, whether this bias is based on bottom up or top down processes. In order to assess the answers to these questions there are three kinds of methods that have been used most frequently. First of all, the visual search task is the experimental version of

searching a face/ or rather a person in the crowd. Here subjects are presented with a number of faces at the same time and their task is to find the happy or angry face among distracter faces (with either the opposite facial expression or neutral faces). Measurements to determine whether happy or fearful faces have an attention benefit, are response times, response accuracy as well as the visual scan paths (recorded with eye tracking). Results have shown a pop out effect of angry faces or happy faces (reviewed in Becker et al., 2011). However, Becker et al. (2011) argue that most of the studies in favor of a pop out effect on angry faces suffer from methodological limitations. Particularly, they argue that these studies used faces (schematic and real pictures) which contain certain low level features that might attract attention, such us the visibility of teeth, or the difference in eye brow orientation. Becker et al. (2011) thus conclude that the results are rather due to an effect of these characteristics than due to the conveyed emotion. They therefore established experiments that avoid such biases and conclude that it is actually happy faces that attract more attention.

However other paradigms as well as neuropsychological evidence from patients with a unilateral neglect syndrome, have added supporting and contrasting evidence. For example, Stein, Zwickel, Ritter, Kitzmantel, & Schneider (2009) have used the attentional blink measure, in which they measured the effect of a neutral or an angry face on the processing of pictures during a rapid serial presentation. A first target is the face, and subjects have to either judge the emotion of the face or categorize the gender. The second target is a visual scene and subjects have to discriminate between indoor and outdoor illustrations. Typically, the judgment on the first picture is detrimental to the detection of the second target. In this experiment, the results show that when the subjects do not have to intentionally process the stimulus as happy or angry, there is no interference of emotion

with the task. They show an effect of angry faces only in the condition in which the task required subjects to judge the facial expression. In this condition the deterioration of the processing of the second stimulus is larger when the first stimulus is an angry face. The authors conclude that the effect of angry faces is under top down mechanisms.

Such effects of angry faces may also occur automatically, though. Neuropsychological evidence shows that patients suffering from a hemi neglect syndrome react to angry faces on the neglected site, and this reaction partly compensates for their deficit. This suggests that angry faces may attract attention through early bottom up processes (Domínguez-Borràs et al., 2012). These findings have been underlined with neuroimaging data in healthy subjects, suggesting an early activation of the amygdala when viewing angry faces (Brassen, Gamer, Rose, & Büchel, 2010).

This variety of results reveals the complexity of these attention mechanisms, especially when it comes to human faces. Supplementary paradigms are needed in order to further investigate the mechanisms. Decoding and understanding these mechanisms is especially important with regard to patients suffering from mental illnesses as for example schizophrenia. These mechanisms are also important to understand how emotion interferes with other cognitive functions. For the same reason, it is also important to take into account possible impairments of face processing in patients. In particular, several studies have suggested that patients with schizophrenia have difficulties decoding emotional expressions. We briefly summarize this data in the following section.

1.5. Facial expression recognition in patients with schizophrenia

As mentioned in the general introduction, patients with schizophrenia have often been described as being less sensitive to emotional stimuli or as less emotional in general. We have also seen that, at a behavioral level, the rating of emotion may not be as dampened as previously believed, although behavioral measure may lack sensitivity. The same debate applies for faces. Again, there is a vast literature on this subject and we will briefly summarize it. A recent meta-analysis on the performance of patients with schizophrenia, has shown that altogether these studies confirm an impairment in facial expression recognition (Kohler, Walker, Martin, Healey, & Moberg, 2010).

These deficits have been shown to be greater when the positive and negative symptoms are more severe, however they do not seem to degrade or upgrade over time (Addington, Penn, Woods, Addington, & Perkins, 2008; Kohler et al., 2010). Thus it has been discussed whether this kind of deficit could be a trait marker. One possible explanation could be linked to a difference in face scan path that has been revealed in patients (although why the scan path is disturbed still needs to be unraveled) (Loughland, Williams, & Gordon, 2002). Patients do not look at the traits which are relevant for emotion perception (e.g. eyes, mouth), as much as healthy controls. Another possible explanation for poor emotion recognition could be a lack of emotional experience, as patients might not be able to interpret the emotional cues in the same way as healthy subjects do.

Regardless of the mechanisms subtending these difficulties, the ability to identify emotional expression is crucial for communication. Impairments have thus been linked to social functioning, independency and work functioning (Hooker & Park, 2002; Kee, Green, Mintz, & Brekke, 2003; Kohler et al., 2010). However, the experimental paradigms that have

been used until today in order to determine such impairments in patients, have been mostly based on identification or differentiation of facial expressions. That means, all these paradigms require some sort of personal judgment or interpretation. There is only scant knowledge on the incidental influence of emotion in patients. Besides, there is nothing in the literature regarding this influence during visual organization.

Since we wanted to explore the interference of emotion on visual organization, we developed a paradigm which measures the incidental distraction of emotional stimuli on a simple cognitive task. The fact that the influence of emotion is incidental makes a large difference relative to the literature on face emotion discrimination in schizophrenia. We will now detail the different steps that were needed in order to develop this paradigm.

1.6. Introduction to our study

To the best of our knowledge there is no experimental paradigm which makes it possible to study the effect of emotion during visual organization. This is why our first step was to create and adapt such a paradigm. We chose to work with a simple but efficient paradigm created by Palmer & Beck in 2007, the repetition discrimination task, which we already evoked above. We will now detail this paradigm and explain how we adapted it to our needs. It consists in the presentation of seven figures (squares and circles) which are aligned horizontally. The figures alternate between circles and squares except in one case: there is always a pair of two figures that have the same shape, right next to each other. The task for the subjects, is to find the pair and to decide whether the pair is composed of two circles, or of two squares. They have two response keys at their disposition, and they respond by pushing the left key for circles, and the right key for squares.

To introduce an organizational factor, Beck and Palmer used different means corresponding to the grouping factors which are part of the gestalt theory. In figure 5, three examples are illustrated: color, common region and connectedness. The different characteristics, such as color or common region, automatically separate the figures into different groups. For example, figures which have the same color are perceived as belonging to one another. The effect of the different gestalt laws is measured via response times. Subjects perceive the targets faster when they belong to the same group, as opposed to the case when they belong to two different groups. In our study we chose to use the grouping factor connectedness.

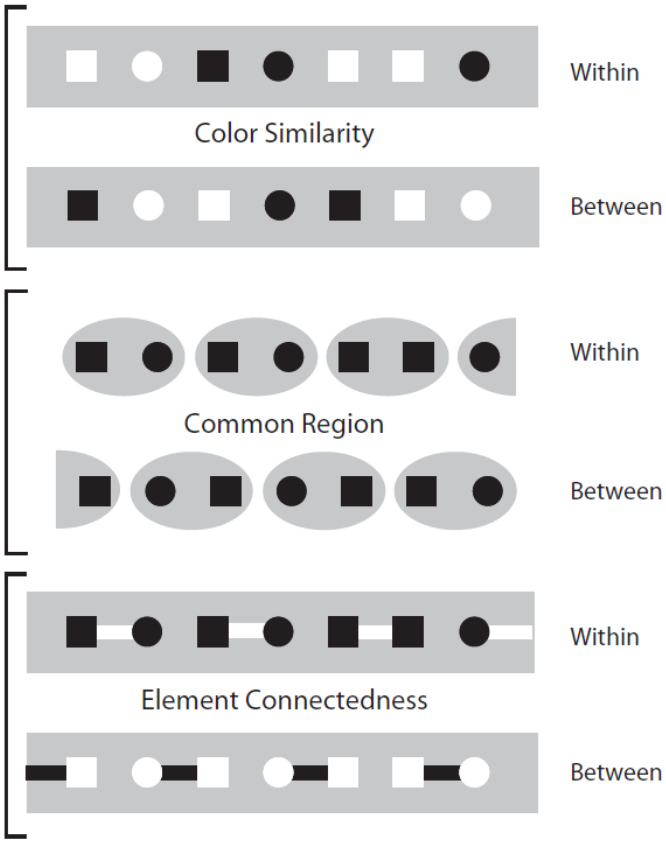


Figure 5. How to study visual grouping, examples taken from Beck and Palmer. The task is to detect the form of the two adjacent figures that are identical. This task is easier if the two figures belong to the same group than if they belong to different groups.

Beck and Palmer have replicated their results several times. This effect is thus quite robust and we felt comfortable to adapt this paradigm to our needs in order to test whether emotion has an effect during this organizational perceptual mechanism (Beck & Palmer, 2002; Palmer & Beck, 2007).

As emotional stimuli we chose to use pictures from the International affective picture system (IAPS) (Lang, Bradley, & Cuthbert, 2008), which is a battery of images with different emotional valence and arousal levels that has been created in 2008. The authors provide a wide range of pictures on different topics, which have all been rated by 100 adult participants on three different scales: valence, arousal and dominance.

The creation of our new paradigm necessitated several stages of adaptation, and in the following we briefly describe the different stages that led us to the final versions of the test.

We started off with negative and positive images in the category 'animals' and created our paradigm by associating a picture to each figure in the row (fig.6).

Figure 6. Example of the association that we created between the geometrical figures and the emotional pictures.

During this process we met several problems. First of all, we could not shrink the pictures infinitely, since the theme had to be very visible. We were thus limited by the size of our monitor. Hence we reduced the amount of figures from 7 to 5. This change however made the task too easy for the subjects. Indeed, the positions of the stimuli on the edges

represent a special case, since one of the figures is clearly visible, and not masked by nearby figures. The pair of targets is thus never located at the edges in the typical paradigm. This means that when there are only five figures, there are only two possible locations for the target pair, which makes the task very easy. Figure 7 represents an example of the possible target locations. Our challenge was thus to complicate the task as to avoid a ceiling effect. First, we added catch trials to the paradigm, for which the targets were located at the edges. This obliged subjects to take into account all possible locations for the targets, although performance during these 'edge' trials, being a special case, was not analyzed. We also made a second modification to our paradigm: instead of keeping the well differentiable forms of circles and squares, we created two kinds of squares, one with sharp and one with rounded edges (fig.7).

This modification did not change the task. Subjects had to find the pair of two figures with the same shape that lie next to each other. To give their answer, they had to press the left key when the target pair was composed of two squares with rounded edges and the right key when the pair was composed of two figures with sharp edges (fig.7).

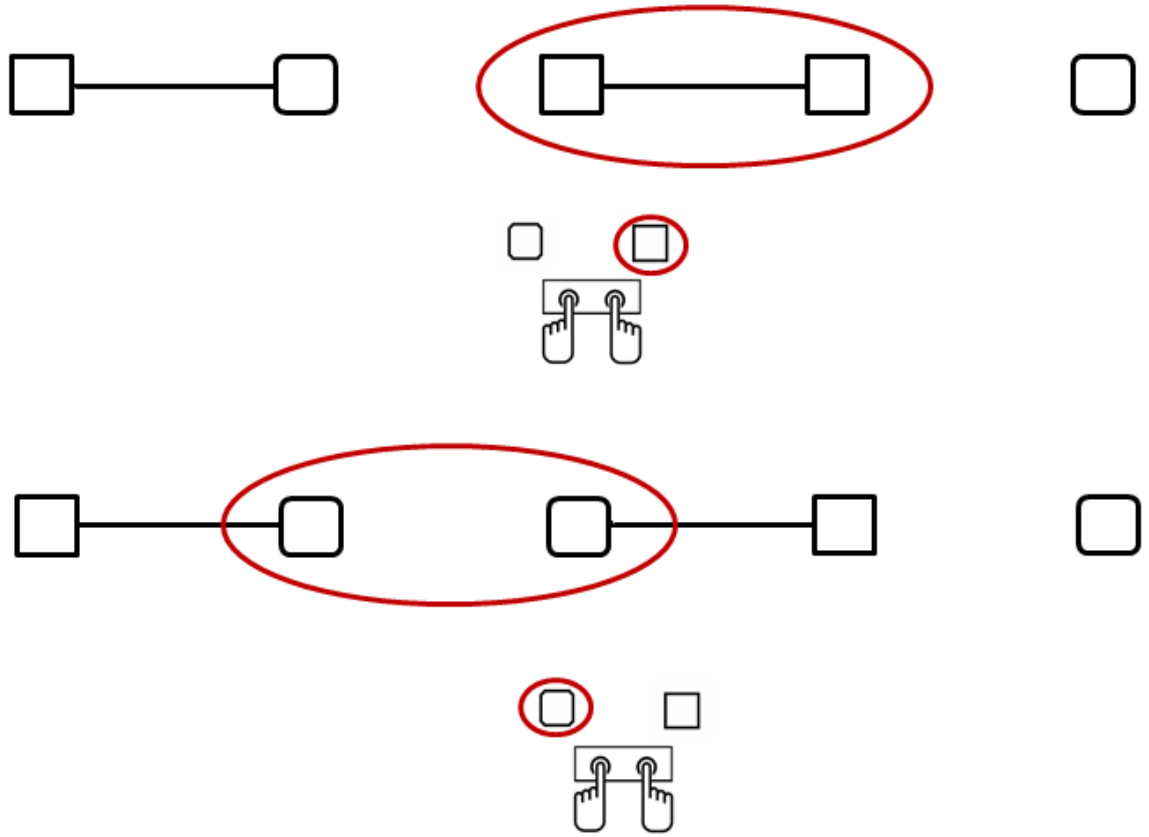


Figure 7. Example of the paradigm we used, the target pair could be composed of two squares with rounded edges or two squares with sharp edges, and be situated either in the middle on the right or in the middle on the left of the figure. The singleton is either on the right or on the left side.

1.7. First set of paradigms

For the first paradigm we chose three animal pictures with a positive valence (dog, butterfly, horse) and three animal pictures with a negative valence (spider, tiger, snake). In the row of five figures, each figure was thus associated to one picture, positive or negative. We established consequently 3 different conditions that were possible as a background configuration of the two figures that form the target pair. The two target figures could be either located on two positive pictures, two negative pictures, or one of each (fig.8). We then added the grouping factor connectedness (Table 3).

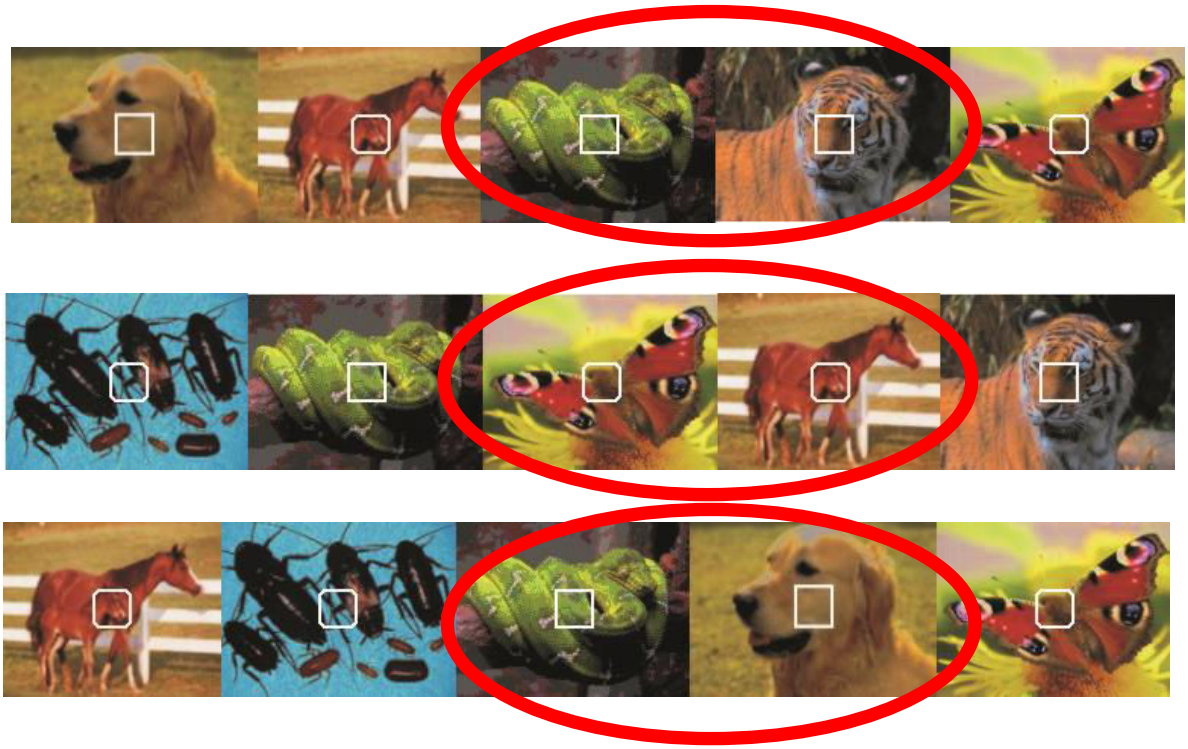


Figure 8. Emotional conditions, targets could be located on two pictures with a negative valence, two pictures with a positive valence, or two pictures with different valences.

In all, there were thus 6 different conditions, connected (within-group) and unconnected targets (between group) on the three different emotional conditions.

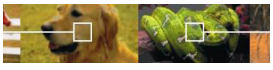
	non congruent	negative congruent	positive congruent
connected			
unconnected			

Table 3. Representation of the six possible conditions used in this paradigm

1.7.1. Control paradigms

In order to control for possible biases that could be linked to the changes that we conducted on the original paradigm, we created two control paradigms. In a first one, we simply left out the bars that induced the factor "connectedness" (fig.9). This procedure allowed us to control for possible effects of the emotion or the characteristics of the images independent of the connectedness effect. Without this factor connectedness, there are 3 conditions in this paradigm: the two target figures could be located on two pictures with a positive image, two pictures with a negative image or one of each.

Figure 9. Example of the paradigm testing the general effect of emotion.

For the second control paradigm we created a homogenous background that had the same luminosity as our original paradigm (fig.10). We chose this control paradigm as to verify whether our paradigm reveals a grouping effect independent of the background pictures. There are only two conditions in this paradigm: either the two target figures are connected, or they are not.

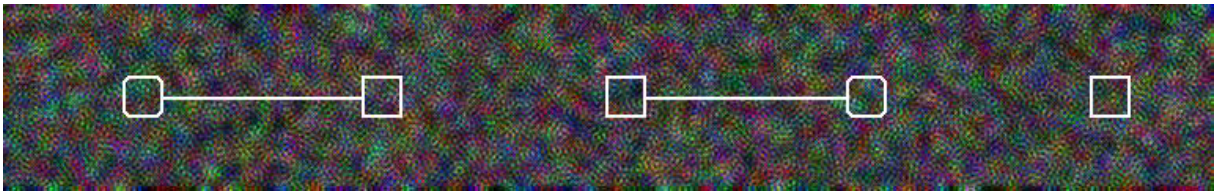


Figure 10. Example of the stimuli used with the aim to test the general effect of connectedness.

1.7.2. Procedure

The different experiences were ran on a laptop, DELL Inspiron 8100 (resolution 800x600; Colour bit depth 16) and programmed using E-prime, a software application suited for conducting experimental psychology experiments, and allowing precise response time encoding. A serial response box connected to the computer allowed participants to give manual responses.

15 subjects were included in this study. Each participant realized the three types of experiments in a random order. They started off with the main experiment and conducted later on the two control experiments. Each paradigm started off with a trial phase which was not taken into account for the analysis.

In the first experiment with the conditions emotion and connectedness, the training consisted of 36 practice trials directly followed by 240 proper trials composed of 192 figures which presented the targets in the middle and 48 with the targets at the border. Since we did not take into account the trials with the targets at the border, this meant 32 trials for each of the six conditions. The 6 pictures, the shapes (squares with sharp and rounded edges) and their location, the conditions “connectedness” (connected vs. unconnected) and the condition “emotion” (congruent positive, congruent negative, or non congruent) were equally represented. The order of the trials was randomized.

In control experiment 1, the purpose was to investigate whether emotional valence could be a grouping factor per se. One run started with 36 practice trials, followed by 120 trials, 96 with the target in the middle and 24 at the border, in random order, i.e. 40 trials per condition. The occurrence of the pictures and figures, as well as their location, were equally represented throughout the experiment.

Control experiment 2 was designed check the grouping effect of connectedness without any other stimuli. There were 48 trials, 40 with the target in the middle and 8 on the border, i.e. 24 trials for each of the two conditions ('within-group pairs' vs. 'between-group pairs'; 12 trials per condition when considering only the first half). Occurrences of the two different shapes as targets and their location were equally randomized.

1.7.3. Results and Discussion

We analyzed the results using multifactor ANOVAs. For the first paradigm with six conditions (factor "emotion" = negative, positive, incongruent and factor "connectedness" = connected and unconnected) analysis revealed a global interaction between the factor "emotion" and the factor "connectedness" ($F(2,28)=5.39$; $p<.05$; $\eta_p^2=.28$), and an effect of "connectedness". There was a general advantage for connected figures (mean RT = 1092 ms) over unconnected figures (mean RT = 1301 ms) ($F(1,14)=27.7$; $p<.0005$; $\eta_p^2=.66$). Since it has been shown that the repeated use of the same emotional stimuli can result in an habituation phenomenon (Codispoti et al., 2006), we separated the first half and the second half of the experiment in order to analyze whether there was an effect in the first half of the test which might have been nullified in the second half. Indeed there was an interaction between the factor emotion, the factor connectedness and the factor time ($F(2,28)=3,32$, $p=.05$; $\eta_p^2=.19$) (fig.11).

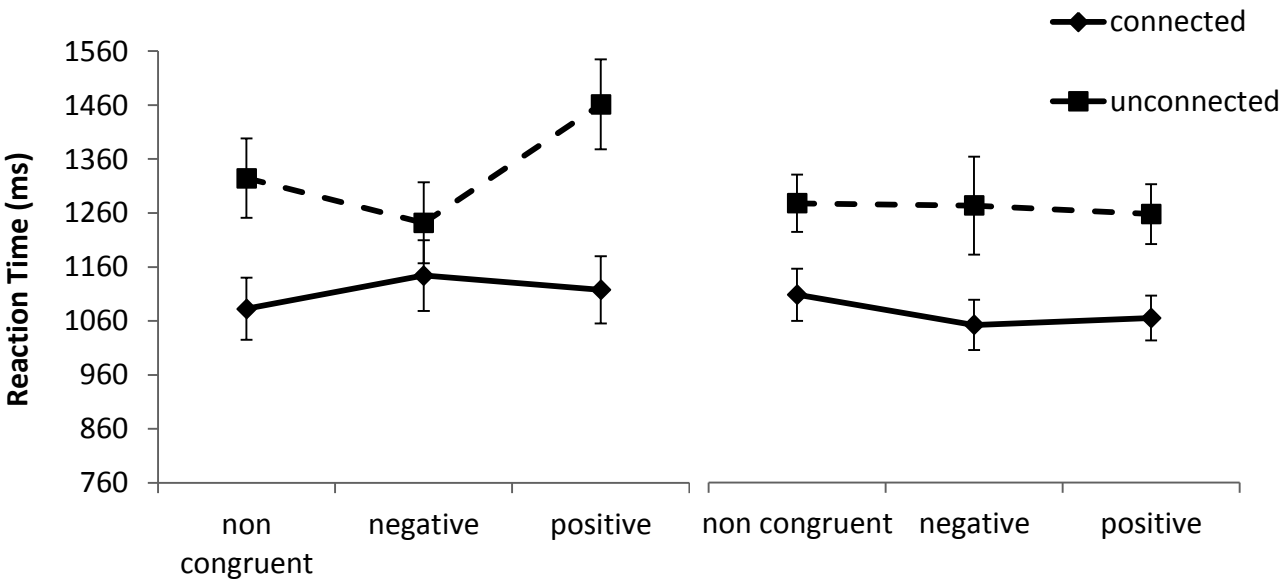


Figure 11. Mean RTs with SEM, showing a difference between the first half of the experiment (left panel) and the second half of the experiment (right panel). In each panel RTs are displayed as a function of the presence of connectors relating the geometrical target figures (plain line for connected vs. dashed line for unconnected targets), and of the emotional valence of the background pictures (non congruent, congruent negative and congruent positive from left to right). The effect of emotion is evident in the first half but not in the second half of the experiment. Here, the effect of grouping vanishes when the targets are associated to two pictures of animals with a negative valence.

We dissected the analysis, and analyzed the interaction of emotion and connectedness for the first half, and the second half, separately. There was an interaction of connectedness and emotion in the first half ($F(2,28)=6.28$; $p<.05$; $\eta_p^2=.31$), and no interaction in the second half ($F(2,28)=.24$; $p=.79$).

We further dissected the interaction in the first half of the experiment in order to determine which emotion interacted with the factor “connectedness”. The effect of connectedness was preserved in case of a positive background ($F(1,14)=13.12$; $p<.005$; $\eta_p^2=.48$) and an incongruent background ($F(1,14)=13.81$; $p<.005$; $\eta_p^2=.5$), but was absent when the two pictures behind the targets had a negative valence ($F(1,14)=2.24$; $p=.16$).

1.7.4. Control conditions

The two control conditions were designed to test the effect of emotion (control 1) and connectedness (control 2) on their own. For control 1 there were thus three conditions corresponding to the emotional background on which the figures were located. We conducted an ANOVA, which revealed no effect of emotion at all (F (2,28)=.32; p=.73) (fig.12).

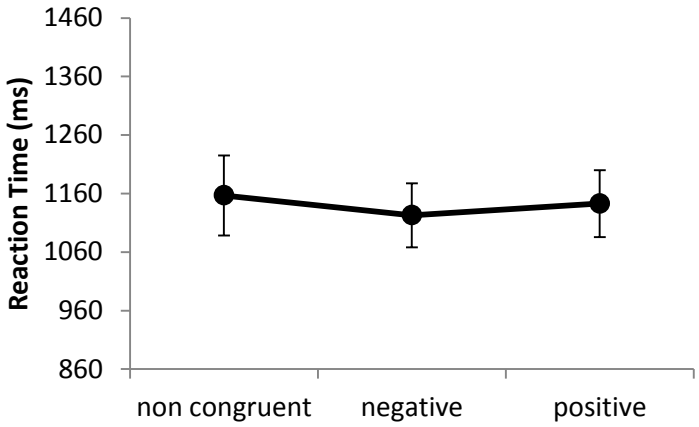


Figure 12. Mean RTs with SEM are averaged over subjects, as a function of the type of emotion (on the x-axis) in the control experiment without connecters. There was no grouping effect of emotion.

For control 2, there were two conditions, connected and unconnected. The ANOVA analysis revealed no effect of connectedness (F(1,14)=.00026 p=.99) (fig.13).

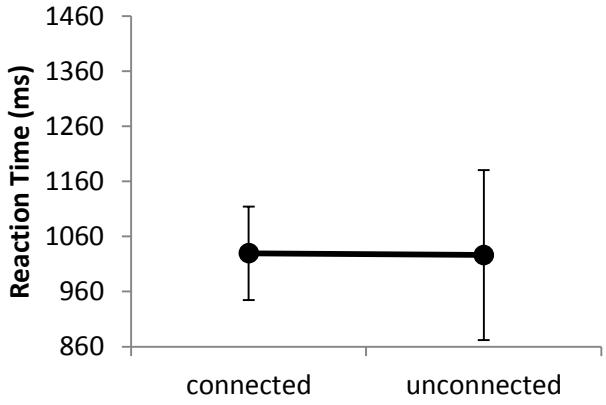


Figure 13. Mean RTs with SEM are averaged over subjects, as a function of the factor connectedness. No effect of connectedness was observed in this control experiment (without the factor emotion).

1.8. Discussion

Considering these results we concluded that there might be an effect of emotion on visual perception. However our control experiments revealed that the task was still too easy. There was no effect of grouping at all in the control task which means that the participants did not really have to search for the target pair. Furthermore the fact that we were only using 6 pictures probably induced habituation and the effect of emotion disappeared after the first half of the trials.

Consequently we wanted to continue this research but we had to optimize our paradigm. We therefore decided to add a complexity factor by changing the position of the figures on the pictures and to limit habituation by taking out the catch trials. In the next paradigm the geometrical figures were therefore positioned in the four corners of the pictures, and position was randomized throughout the paradigm. In order to replicate our results, to further limit the effect of habituation and to widen our research field, we added three other kinds of stimuli. For this paradigm we chose the categories: animals, faces, objects and social scenes. The results of this first study guided the way we pursued this research. We conducted further experiments in the two categories faces and animals. We confirmed the effect of negative animal pictures on this task in a further study which is presented in the annex for a detailed description. Here we will continue with the category faces and detail the series of experiments conducted with these stimuli.

A last important factor that had to be considered with these kinds of results, is the subjective experience of emotion which can vary for each individual and each stimulus. The images we used had been evaluated by a cohort of 100 people, however the pictures were not very modern and were only evaluated in the United states. In order to control for

differences that might be observed in respect to culture or time, we added a measure for the subjective evaluation of the pictures to our following paradigms.

Chapter 2:

Emotional stimuli interfere with visual organization

Emotional stimuli interfere with visual organization

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Abstract

Access to information is faster and more efficient within a group of connected objects than across different groups. This advantage results from visual grouping i.e. early and robust mechanisms required for the combination of features and objects. Here we explore whether background objects with an emotional content facilitate the access to grouped objects by attracting attention towards them, or whether they will hinder this effect through distraction. Subjects had to identify a pair of identical and contiguous targets, embedded in a row of five figures. The target pair could be either connected through a horizontal line or not. Here we added background pictures with an emotional content to the paradigm which were not relevant for the task. Nevertheless, the results show an inversion of the advantage provided by grouping when the background is composed of faces with a positive emotional content. Thus in this situation, connectors were detrimental for the search of targets, despite the fact that they were highly contrasted and in the foreground. Saccades on positive faces were longer, suggesting that these faces take priority over the connecters and that the connecters hamper the exploration of faces instead of guiding it towards the targets. The results suggest that positive faces can disturb visual guidance of automatic grouping, by interfering with visual form exploration. .

Key Words: emotion, visual perception, visual organization, automatic grouping, connectedness

Introduction

The human visual system is designed to extract salient information rapidly and ensure survival. This requires an efficient way to identify forms and mechanisms allowing us to evaluate the saliency of information regarding our current goals and tasks. Thus automatic grouping mechanisms enable the identification of object forms, and emotion processing contribute to the identification of object saliency. Both aspects are important for the exploration of the visual world. However, they are usually considered independently from each other. Our goal here is to identify how emotion information contributes or interferes with the organization of visual information. We will first shortly review the impact of grouping mechanisms and emotion processing separately, and introduce our study subsequently.

Grouping mechanisms

Visual perception starts with the encoding of primitive visual information such as orientation, contrast, color and luminance, which are processed locally in the primary visual cortex. Subsequently, through integration of this information in higher visual areas and feedback connections, objects are identified and their relations coded, allowing the visual percept of our environment to emerge (Hubel & Wiesel, 1977; Kandel, Schwartz, & Jessell, 2000; Livingstone & Hubel, 1988; Roelfsema, Lamme, & Spekreijse, 2000; Tanaka, 1993). One important step in perceptual organization is grouping. Contours have to be organized in the right way to perceive objects, which in turn have to be organized to structure the visual scene properly (Kandel et al., 2000; Palmer & Rock, 1994; Wertheimer, 1923). Thus in every visual scene, the stimuli have to be either grouped together, or separated from one another: for example in order to realize that our finger is NOT part of the slice of bread we are eating.

Different automatic grouping factors as for instance “color”, “similarity” and “collinearity”, have been described and widely explored (Palmer & Rock, 1994; Wertheimer, 1923). They guide visual search and exploration. As a matter of fact it is easier to detect diverse information within a unique object than across different objects (Duncan, 1984; Egly, Driver, & Rafal, 1994). In addition automatic grouping through color or connectors has been shown to attract attention. In particular, shortened fixation latencies and increased fixation duration have been shown for grouped information (Anderson, Heinke, & Humphreys, 2012; Giersch & Rhein, 2008). Most grouping mechanisms are very robust. However, they are still flexible (Beck & Palmer, 2002): several behavioral studies have shown that the processing of information in the primary visual cortex can be influenced by e.g. contextual information (Beck & Palmer, 2002; Van Assche, Gos, & Giersch, 2012). The importance of feedback connections on the primary visual cortex may at least partially subtend this plasticity (Bullier, 2001), although later mechanisms may also intervene (Van Assche, Gos & Giersch, 2012).

Here we used the repetition discrimination task created by Palmer & Beck (2007) which provides an easy way to evaluate the strength of grouping and can be considered as a simplified version of a visual scene. It includes a horizontal array of very simple geometrical figures, within which subjects have to find and identify two figures that are identical and next to each other. We chose the grouping factor “connectedness” and used line segments to physically join the figures. This leads to a prioritization of connected over unconnected figures, and helps to find and identify the target figures faster when they are part of the same group than when they belong to different groups. Interestingly, this advantage can be modulated (Beck & Palmer, 2002; Giersch & Rhein, 2008; Giersch, Van Assche, Capa, Marrer, & Gounot, 2012; Giersch, Van Assche, Huron, & Luck, 2011; Van Assche & Giersch, 2011; van Assche et al., 2012; Vickery, 2008). For example the advantage increases when the

percentage of connected target figures within an experimental block is higher than the percentage of unconnected target figures (Beck & Palmer, 2002; Van Assche et al., 2012). However, this advantage for automatic grouping can be more easily increased than reversed. In fact, it can usually be reduced but not reversed (Giersch et al., 2012; Van Assche et al., 2012). This highlights the robustness of automatic grouping processes, which subtend our ability to isolate objects from the background and guarantee the stability of our visual organization of the environment.

These well-established mechanisms of grouping might lead to the conclusion that automatic grouping reliably guides us through the world around us. However, it is not the only factor guiding our visual exploration. Pictures with an emotional content can also be a powerful mean to orient attention. We shortly review the evidence for an impact of emotion in the next paragraph

Effects of emotion

Over the past years, several theories have evolved on how emotion influences visual perception. For example, Vuilleumier & Huang (2009) have shown that the allocation of attention can be regulated as a function of the emotional significance of the stimulus. Here we will focus on the effects of emotional faces, since this is the stimulus category which led to the clearest results in our studies. Faces have been used in a range of paradigms to investigate their power to attract attention. It has been checked to which amount they facilitate stimuli detection or degrade performances by distracting from nearby information. These studies highlight the importance of several methodological and interpretation difficulties when using emotional stimuli, which had to be considered here.

The physical characteristics of the stimuli as well as the paradigm that are used to incite emotion have to be considered. A large body of work suggests that stimuli conveying fear or anger emotions may best attract attention. A well-known effect is the 'face-in-the-crowd' effect, whereby angry faces are detected faster than happy faces when presented among distracter faces (Shasteen, Sasson, & Pinckham, 2014, but see Becker et al., 2011). This effect is corroborated by studies in spatial neglect syndrome. They show that emotional stimuli (faces, voices, visual scenes) partially compensate for the spatial neglect and attract attention automatically (review in Domínguez-Borràs, Saj, Armony, & Vuilleumier, 2012). The results in brain-lesioned patients convincingly suggest that emotions, especially negative emotions are processed pre-attentively (in the neglected field) and automatically attract attention.

However, at least two difficulties should be considered when applying these paradigms to healthy volunteers. First, it is difficult to disentangle an effect of the perceptual characteristics of the faces from an effect of their emotional content. Indeed, an open mouth and white teeth may attract attention because they represent a highly contrasted signal rather than a salient social message. Such a perceptual advantage may mediate some of the advantages for happy and angry faces observed in the literature (Becker et al., 2011). Such effects can be expected to persist even in case of face inversion, when facial expressions are made unreadable (Miyazawa & Iwasaki, 2010). It should be noted that in healthy volunteers advantages for happy faces are still observed even when low-level differences are controlled for (Becker, Anderson, Mortensen, Neufeld, & Neel, 2011; Calvo & Nummenmaa, 2009), suggesting that low-level features should be taken into account but do not seem to be the sole cause of the effect triggered by emotional faces.

Furthermore, the influence of emotion may be gated by task requirements and attentional control settings. Barratt & Bundesen (2012) have used a flanker task, in which subjects have to discriminate a target flanked by distracters. The distracters were schematic faces with positive, negative or neutral expressions, and the results show that negative faces interfere with the central target. However, this occurs only when the central target is a face itself. It has no effect if targets are letters to be discriminated. A similar result has been observed with an attentional blink paradigm and with face photographs (Stein, Zwickel, Ritter, Kitzmantel, & Schneider, 2009). The presentation of a fearful face within a series of rapidly presented stimuli induced a large attention cost and impaired the detection of a following target. However, this occurred only if subjects had to indicate the emotion of the face, and disappeared if they only indicated its gender. These two studies suggest that the task set gates the influence of emotion. Yet, they cannot discard a more incidental influence of emotions. Indeed the use of schematic faces made the flanker task very easy, with response times around 500 ms. In rapid serial visual presentation tasks (RSVP), the presentation of faces is not very close to every day conditions, in which there is ample time to explore a face.

All in all the literature shows that emotional face processing interferes with visual tasks and orients attention, but the mechanisms of the effects, as well as the differences between angry and happy faces are still a matter of debate. Moreover, to the best of our knowledge, possible emotion interferences during visual organization have not been explored. This all makes it difficult to predict how visual organization can be modulated in the presence of emotional information.

Interference of emotional processing during visual organization

As we have seen there are several mechanisms of attention orientation, including both automatic grouping and emotional processing. It can thus be questioned how these two mechanisms of attention guidance jointly contribute to our access to visual information. Here we explore to which amount automatic grouping resists to the presence of background pictures with an emotional content. In respect to the impact of emotional stimuli on visual perception and their saliency, we hypothesize that they may interfere during perceptual organization.

We adapted the repetition discrimination task (Palmer & Rock, 1994) to our needs and added stimuli with an emotional valence so that targets were superimposed on positive negative or neutral pictures. We used photographs rather than schematic stimuli but avoided high contrasting characteristics, especially in faces. An effect of emotion on visual organization was expected to be reflected in a variation of the advantage provided by grouping. This task differs in many aspects from paradigms used to explore the influence of emotion. First, it measures the advantage of grouping, which is usually not considered in the emotion literature. Second, the task requires not only visual search and form exploration, but also the discrimination of two figures. It requires thus additional processing, i.e. comparison and exploration of different figures, which leaves way for different interference effects by emotional stimuli. Finally and consistent with this, the pictures stay on the screen until the response of the subjects. They are thus presented for a much longer time than in attentional blink or the RSVP, which entails thereby a longer exploration of the stimuli.

There were several ways in which emotional processing could interfere during this task. First, we could not a priori exclude the possibility that emotional processing would

interfere directly with grouping itself. There is indeed both neural feedback connections between the amygdala and the primary visual cortex (Freese & Amaral, 2006), and EEG evidence for early emotional biases in the processing of visual information (Pourtois, Grandjean, Sander, & Vuilleumier, 2004). Second, and more likely, emotional pictures could interfere with visual organization by attracting attention, which leads to the following question. Would this effect reinforce the advantage provided by automatic grouping, or degrade it? An additional question was whether positive or negative faces would have similar or different effects. As we have seen, it is hard to make a clear prediction from the literature. With the aim of providing a response to these questions, we created and conducted five successive experiments. In the first experiment we used different picture categories and the results showed that visual organization was affected most clearly in the category faces. For this reason, we focused on faces in the following paradigms.

Material and Methods

The overall structure of the paradigm was the same for each experiment.

General method

Participants. Subjects were unmedicated and had no history of psychiatric or neurological illness. Visual acuity as well as color vision was tested, using the Freiburg Visual Acuity Test and the Baby Dalton. All subjects had normal color vision and a normal or corrected to normal visual acuity.

Equipment. All experiments were run on a laptop, Dell Inspiron 8100 (resolution 800x600; Color bit depth 16) and programmed using E-prime 2. In order to measure exact

response times we used the e-prime response box. There was a distance of 60cm between the subject and the screen.

Stimuli. For this study, we adapted the original repetition discrimination paradigm with the grouping factor "connectedness" by Beck and Palmer (2007). Stimuli displayed on each trial were composed of a row with five squares made of white outline contours. Squares had either rounded or sharp edges (0.6 x 0.6° of visual angle; 1° of visual angle corresponds to 1cm on the screen when the subject is at a distance of 57cm from the screen). These squares were evenly spaced (3.6° of visual angle between each figure center) alternating sharp and rounded edges, with only one repetition, i.e. two adjacent squares that shared the same shape (fig.1). The pair of identical adjacent figures represented the target, and subjects had to decide whether these figures were squares with sharp or rounded edges. The target pair could be located in the middle right or middle left part of the target row. Like in the original paradigm (Palmer & Beck, 2007), we excluded the possibility to draw targets on the rim because these figures are special: they are not surrounded by two but only flanked by one other figure and picture.

The factor "grouping" was manipulated by means of connectedness. We used 3° long white bars, which connected the figures by pairs. As a consequence the two identical squares of the target pair were either connected, or unconnected in which case the bars connected the two target squares to their non-identical neighbors.

The factor emotion was manipulated by means of pictures with an emotional content that we added in the background of each geometrical figure. Thus the two target figures were located on two pictures with either an identical emotional valence (negative congruent, positive congruent), or different emotional valences (non congruent: one picture

negative/one positive). In order to preserve the visibility of the emotional pictures, we reduced the original paradigm with seven geometrical figures in a row (in the paradigm of Beck & Palmer, 2002), to only five figures in a row. Very small emotional pictures would have made their processing difficult, especially the processing of their emotional character. As a consequence of this variation the task became easy. To compensate for this, we firstly alternated the location of the squares on the pictures between the four different corners (Fig.1) and secondly employed squares with rounded vs. sharp edges rather than plain circles and squares, which made it more difficult to discriminate the target forms.

The whole group of figures (squares and emotional pictures) was located in the middle of the screen and the background was white.

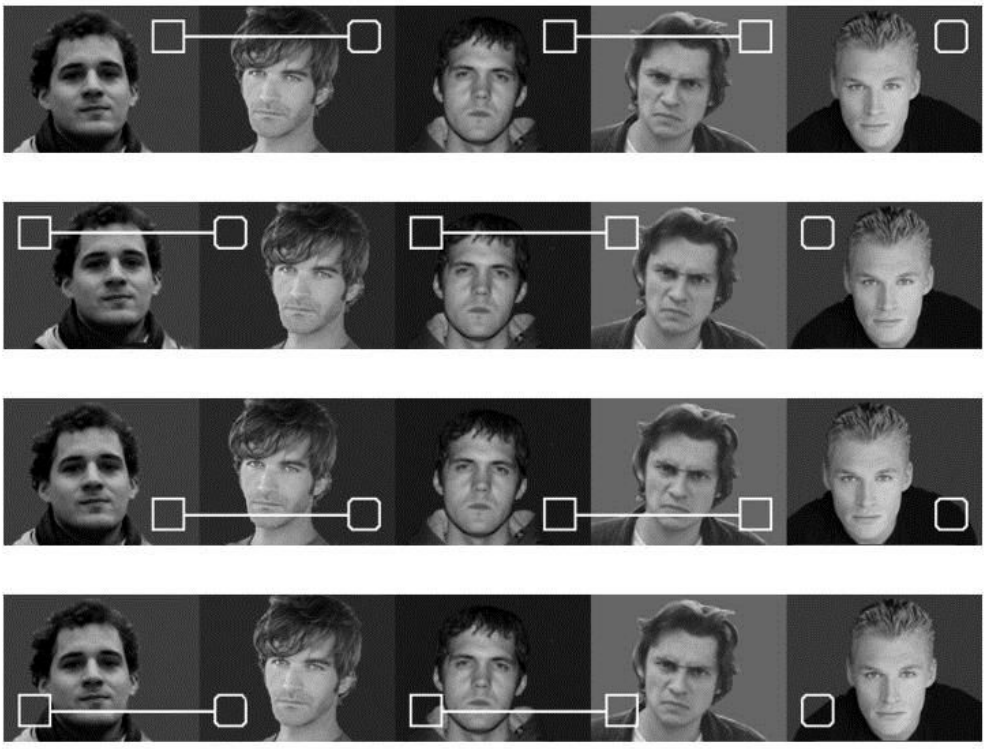

Figure 1. Examples of the different target locations (here in black and white)
We reduced the original paradigm from seven to five figures in order to keep the background pictures visible. To compensate for this loss of complexity, the squares and circles could be located in one of the four corners of the background pictures. The background pictures illustrated in this figure are not the originals. We created these examples in order to respect the publication conditions for the use of the IAPS picture database (Lang et al., 2008). Like for the originals, pictures with a positive valence (two left-most pictures and one rightward picture) are not necessarily those with a positive expression.

Emotional pictures. The pictures were all chosen from the International affective picture system (IAPS) (Lang, Bradley, & Cuthbert, 2008). Positive: 1410, 1604, 1710, 2500, 2630, 2005 5831, 8400, 8499, 5450, 5480, 7580; negative: 1050, 1930, 1280, 2100, 2120, 2110, 2703, 6821, 9413, 1275, 6200, 9010; neutral 2190, 2200, 2210, 2214, 2493, 2495. In order to verify whether the participants in our experiments feel the typical way about the emotional stimuli, we asked them to rate valence and arousal levels for each picture used in the paradigm. We used the same rating instrument as Lang et al. (2008), i.e. the self-assessment manikin (SAM). The SAM consists of a row of graphic figures that range from smiling and happy to frowning and unhappy, thus representing the hedonic valence

dimension. For the arousal dimension, SAM figures range from relaxed and sleepy to excited and wide eyed (Bradley & Lang, 1994). We adapted the figures to our needs by integrating them into a software program (e-prime 2) which we designed for our purpose.

After the main experiment, subjects saw each emotional or neutral picture individually for five seconds and rated valence and arousal levels successively. Participants indicated their feelings by clicking with the mouse on the location corresponding to the manikin with the right facial expression. We calculated mean arousal and valence ratings for each subject and analyzed differences among individuals. Subjects who deviated from the mean more than twice the standard deviation were excluded from the whole analysis (1-3 subjects per experiment). Apart from that we compared mean valence and arousal levels for the IAPS pictures between our population and the one provided by the IAPS with a student's t-test. There was no significant difference (Table 1).

VALENCE	**1** IAPS ratings	**2** IAPS Norm	**t-test**
Neutral	4.87 (1.36)	5.06 (1.16)	t= -.71 p= .48
Positive	5.95 (1.47)	6.10 (1.59)	t= .84 p= .4
Negative	2.98 (1.19)	3.0 (1.52)	t= -.08 p= .94

AROUSAL	**1** IAPS ratings	**2** IAPS Norm	**t-test**
Neutral	3.13 (1.6)	2.97 (1.95)	t= .47 p= .4
Positive	2.89 (1.6)	3.19 (2.02)	t= -.86 p= .39
Negative	4.95 (1.94)	4.85 (2.46)	t= .23 p= .82

Table 1. Comparison of picture ratings between the two populations
Using a student's t- test we compared the mean valence and arousal ratings that we obtained after each experiment for the three positive, three negative and six neutral IAPS pictures, to the norm provided by the IAPS. The differences in valence and arousal levels are not significant (last column on the right).

Procedure

Participants had to locate the pair of identical squares in between the target row in order to decide which shape it was made of. Subjects answered by pressing the left button of the e-prime response box when the pair was composed of two squares with rounded edges and the right button when the pair was composed of two squares with sharp edges. The emotional pictures were thus irrelevant and their effect on the task can only be incidental.

On each trial, a little black dot was displayed for 250 ms in the center of the screen as a fixation point in order to reorient the participants' vision to the center. The pictures were displayed after a new delay of 250 ms and stayed on the screen until the participants gave their response. They were instructed to push the corresponding button as fast as possible

and without mistakes. No feedback was provided. A new trial started 250 ms after the subject response.

Each test was preceded by 16 training trials in order to make sure that the subjects understood the instructions properly. After the test, subjects rated each picture on pleasure and arousal levels. The quantity of the trials varied across experiments, depending on the number of conditions. This information is thus detailed for each experiment. All characteristics of the stimuli were equally represented across trials i.e.: the shape of the target figures (squares with rounded or sharp edges), the four possible positions of the geometrical squares on the pictures, the position of each picture in the picture sequence (from left to right), the combination of the two pictures behind the target pair and the side (left/right) of the target pair. The order of the trials was randomized automatically for each subject.

Data Analysis

We performed analyses on median response times (RTs) of correct responses and on error rates. It is to be noted that no significant gender difference was observed, neither for emotional ratings nor for RTs. Hence we pooled results across male and female subjects. The same held for all experiments. Analyses of Variance (ANOVA) were conducted on RTs followed by a Tukey post-hoc test. Results were confirmed with sub-analyses, all aimed at dissecting the interactions.

Experiment 1

Experiment 1 was designed to explore whether or not the advantage provided by grouping by connecters can be modulated in the presence of pictures from different categories with a positive or negative emotional valence.

Method

We started off with emotional stimuli belonging to four different semantic categories, i.e. images of social interactions, animals, objects and masculine faces. For each category we selected three pictures with a negative valence and three pictures with a positive valence which did not differ in arousal levels. These pictures were then used as background for the geometrical figures. Pictures from different categories were never mixed up, meaning there was only one semantic category represented on each trial. Each picture was put in the background of one square resulting in six different conditions for each category: the two target figures could be located either on two positive, two negative or two non congruent pictures (factor “emotion”), and each of these pair types could be connected or unconnected (factor “connectedness”,). This leads to a total number of 192 trials: 4 categories x 2 pair types x 3 emotion backgrounds, with 8 trials per condition.

The pictures were all taken in a natural environment and their backgrounds were manipulated manually in order to control for the contrast between background and squares. For the categories “objects” and “social scenes” a simple brightening or darkening operation was sufficient, whereas the backgrounds in the categories “animals” and “faces” were too unequal, and were replaced by a uniform color. For the category “faces”, we chose a different background color for each face in order to physically separate emotional faces from each other. This way each geometrical figure was set inside one of the pictures with an

emotional face. We chose the colors green, ocher, blue, purple, brown, grey, and took care to use the same luminance for each background.

Results and discussion

Fifteen students (9 women, 6 men; mean age 24 years) of the University of Strasbourg took part in the first study. There were three intra group factors: “connectedness” (connected vs. unconnected), “emotion” (positive congruent, negative congruent, non congruent), and “semantic category” (social interactions, animals, objects and masculine faces).

The mean RT was 1041 ms and the mean error rate 7.5%. The ANOVA showed an overall effect of grouping, [connected targets = 971 ms vs. unconnected targets = 1045ms; difference =74 ms; $F(1, 14)=9.75$, $p<.01$; $\eta_p^2=.41$], as well as an interaction between the factors “connectedness”, “emotion” and “semantic category” [$F(6, 84)= 4.9$, $p<.001$; $\eta_p^2=.26$].

We dissected this 3-level interaction by checking the interaction between the factor “emotion” (negative congruent, positive congruent, non congruent) and the factor “grouping” (targets connected vs. unconnected) in each “semantic category” individually. This interaction was significant in the categories masculine faces [$F(2, 28)=12.43$, $p<.0005$; $\eta_p^2=.47$], and animals [$F(2, 28)=5.13$, $p<.05$; $\eta_p^2=.27$], but not in the categories social interactions [$F(2, 28)=.35$, $p=.71$; $\eta_p^2=.02$], or objects [$F(2, 28)=1.90$, $p=.17$; $\eta_p^2=.12$].

The interaction between “grouping” and masculine faces was the strongest, which is why we focus on faces in the further studies.

We conducted a post-hoc HSD Tukey test following the ANOVA analysis on masculine faces which singled out a significant effect of the factor connectedness when the

two targets are associated to a positive background (connected targets= 1101 ms vs. unconnected targets = 933 ms; difference = 168 ms, p<.05) (fig.2). This result was confirmed by a sub-analysis conducted on each "emotion" condition [the sub-analysis conducted on positive faces showed a significant advantage for unconnected targets [F(1, 14)=5.82, p<.05; η_p^2=.29], whereas the sub-analysis conducted on negative faces showed a significant advantage for connected targets [F(1, 14)=12.8, p<.005; η_p^2=.48]; there was no effect in the non congruent condition [F<1].

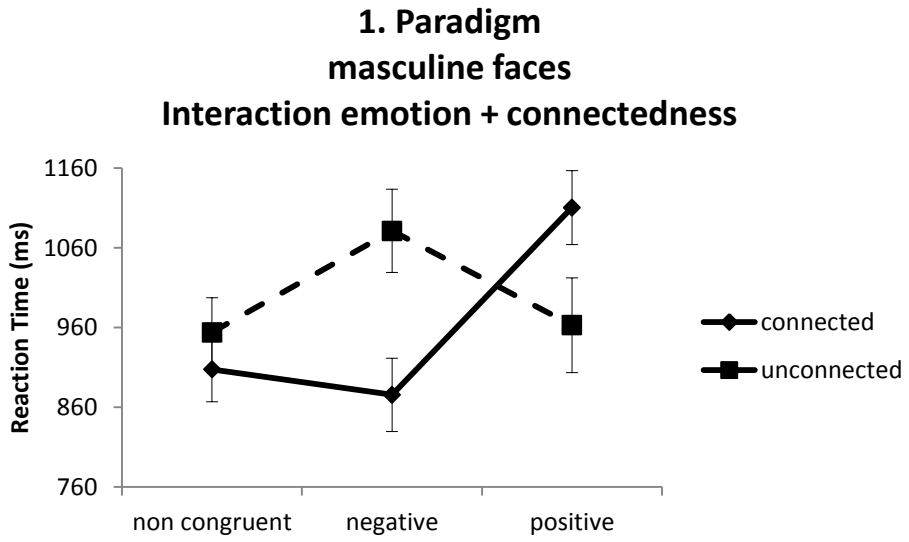

Figure 2. Graph depicting the results of the first experiment in the "semantic category" masculine faces
Mean RTs with SEM, averaged over subjects, as a function of the type of emotion (on the x-axis). The dashed line stands for unconnected targets and the continuous line for connected targets.

Similar results were observed on error rates. There was an interaction between "connectedness" and "emotion" [F(2, 28)= 4.2, p<.05; η_p^2=.23], and a tendency towards an interaction between the factors "connectedness", "emotion" and "semantic category" [F(6, 84)= 2.1, p=.057; η_p^2 =.13]. Sub-analyses showed an interaction between "connectedness"

and "emotion" for faces [F(2, 28)= 6.3, p<.01; η_p^2=.31]. The post-hoc analysis did not show significant results, but sub-analyses conducted on each 'emotion' condition showed an advantage for connected pairs in the non congruent condition [by 7.5%, F(1, 14)=9.9, p<.01; η_p^2=.42], no effect in the negative condition [F<1], and an advantage for unconnected pairs in the positive condition [by 8.3%, F(1, 14)=10, p<.01; η_p^2=.42 (fig.3).

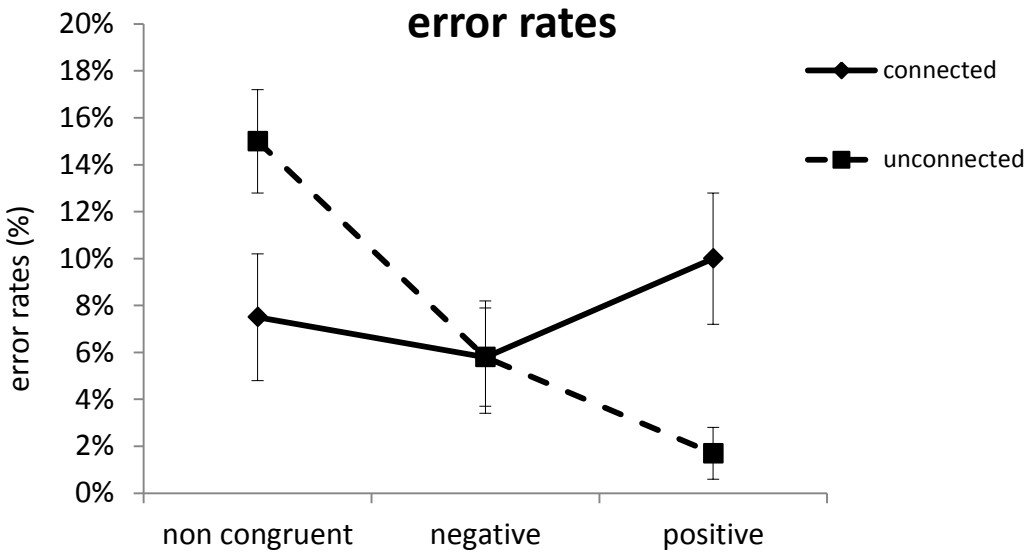

Figure 3. Graph depicting the error rates in the first experiment in the "semantic category" masculine faces
Mean error rates with SEM, averaged over subjects, as a function of the type of emotion (on the x-axis). The dashed line stands for unconnected targets and the continuous line for connected targets.

All in all, an advantage in terms of either RTs or error rates was observed for connected target pairs in the non-congruent and negative emotion conditions, thus replicating the advantage derived from automatic grouping, as described in the literature (Beck & Palmer, 2002; Palmer & Beck, 2007; Van Assche & Giersch, 2011). However, the advantage provided by automatic grouping was reversed when the background pictures

where two positive faces as. This result is surprising given the robustness of automatic grouping. The following experiments were designed to replicate the effect and to check for possible confounds. In particular we had to check whether the effect of positive faces was related to their emotional content or to some other characteristic of the pictures.

Experiment 2

We used the same stimuli as in the preceding paradigm, and added a control condition in which we replaced each emotional face by a neutral face (fig.4).

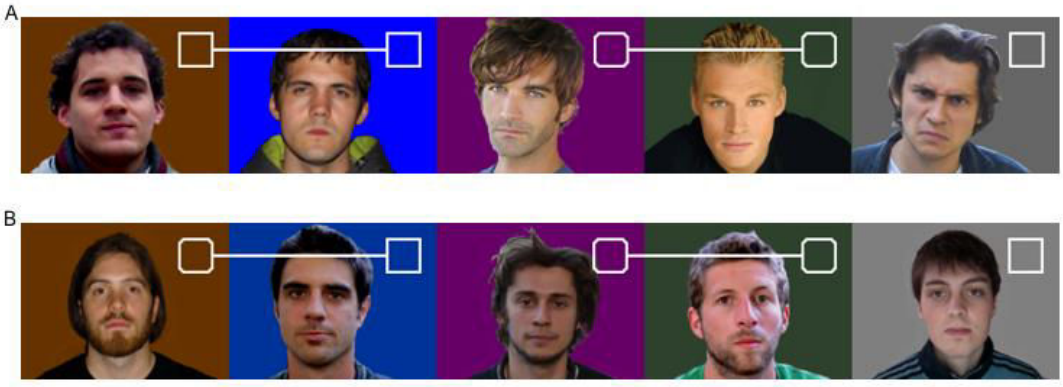

Figure 4. Stimuli substitution for the creation of a neutral control condition
To control for any artifact due to the background, we created a control condition for which we replaced each face with an emotional valence of the original paradigm ***A***, with a neutral face ***B***.

Method

The procedure was the same as in the Experiment 1 with some slight changes related to the addition of neutral faces. We used the same background for emotional and neutral faces, and divided the neutral trials into sub-conditions corresponding to those used with emotional pictures, i.e. the same as in Experiment 1. Thus in total there were three factors: the factor 'connectedness' (targets connected vs. unconnected), types of pictures (emotional

vs. neutral faces) and the factor 'emotion' (non congruent vs. positive congruent vs. negative congruent). This made it possible to analyze the results in exactly the same way for trials with neutral and emotional faces. To get more trials per condition, we increased the number of trials and added a pause for the subjects at half time. This led to a total of 288 trials (12 conditions with 24 trials per condition). If the effects observed in Experiment 1 are due to the background, then similar effects should be observed with neutral faces. In contrast, if the results are due to the emotional valence of the faces, the effect should disappear with neutral faces.

Results and discussion

Again, 15 students of the University of Strasbourg (6 women, 9 men; mean age 24 years) participated in this experiment. The mean RT was 873 ms and the mean error rate 5.6%. The ANOVA demonstrated an interaction between the grouping factor "connectedness" (targets connected vs. unconnected)", the "type of pictures" (emotional vs. neutral faces), and "emotion" (congruent positive, congruent negative, non congruent, named as such for the sake of simplicity, even if there was no emotional valence in the condition with neutral pictures) [$F(2, 28)=3.64$, $p<.05$; $\eta_p^2=.21$] (fig.5). Like in Experiment 1, we dissected the 3-level interaction and analyzed the interaction between the factor "emotion" and the factor "connectedness" for each "type of pictures" (emotional vs. neutral faces) individually. This interaction was significant only for emotional pictures [$F(2, 28)=6.01$, $p<.01$; $\eta_p^2=.3$]. The subsequent post-hoc analysis revealed a significant difference in the emotion condition positive congruent (connected targets = 893 ms vs. unconnected targets = 826 ms; difference=67 ms; $p<.05$). With the aim to confirm this post-hoc analysis we conducted a sub-analysis on the condition with positive faces, which showed a trend towards an

advantage for unconnected targets [F(1, 14)=3.52, p=.082; η_p^2=.2]. No effect was found in the other emotional conditions.

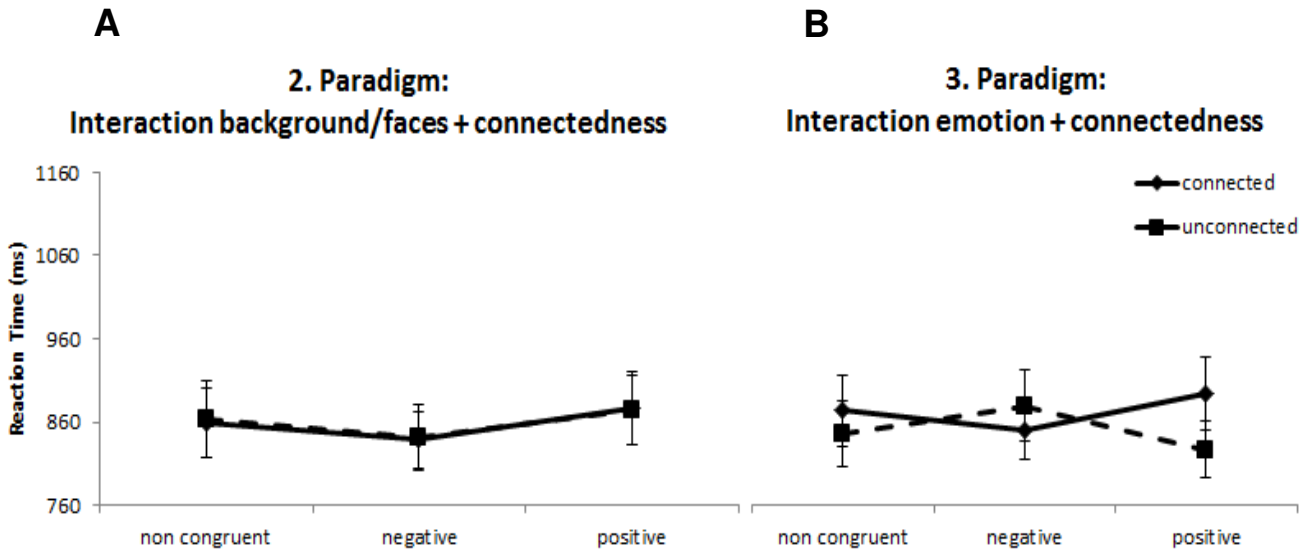

Figure 5. Illustration of the results for Experiment 2

RTs with SEM are averaged over subjects and represented as a function of the emotional valence of the two pictures that lie behind the targets (on the x-axis), and of the two grouping conditions (dashed line = unconnected targets; continuous line = connected targets). Non congruent signifies that the targets are placed on one negative and one positive picture. The grouping effect is reversed only in ***B,*** when the targets are located on two positive faces.

In the control condition ***A*** (with neutral pictures), there was no interaction between the factor "connectedness" and the factor "emotion" corresponding to the background [F (2, 28)=.03, p=.98; η_p^2=.002]. These results indicate that the inversion of the grouping effect is due to the emotion conveyed by the pictures rather than an artefactual consequence of the background.

The analysis on error rates showed a small but significant overall advantage of 3% for unconnected over connected targets [F(1, 14)=16.7, p<.001; η_p^2=.54]. There was no interaction with emotion or type of pictures.

As to further investigate the relationship between the emotional valence and the effects of connectedness, we conducted an analysis of correlation between the valence and arousal levels judged by the participants and their results in each condition of the paradigm. We combined the results for the two paradigms 1 and 2 in order to increase the number of participants. The results show that there is a negative correlation between the evaluation of the positive faces and the rapidity to detect 'unconnected targets' with a positive background. The more the participants judge the emotional valence as positive, the faster they are (N=30/30; r=-.49; p=.006).

No other correlation was detected, not for the other conditions, neither for the arousal evaluations.

All in all Experiment 2 does not show the usual effect of automatic grouping. There is even a slight advantage for unconnected pairs in error rates. The lack of advantage for connected figures might be explained by the fact that the task is very easy, as shown by the response times which are much shorter than in Experiment 1. Background pictures were all in the same category (which was not the case in Experiment 1), and subjects may have filtered this distracting information more successfully. Since there are only two possible locations for the targets, the easiness of the task might have masked the usual advantage provided by connectors. However, despite the short response times, RTs again changed significantly when positive rather than negative or non congruent pictures were behind the targets.. The effect of positive faces was thus replicated across the two experiments, despite the variations in the paradigm and the grouping effect. Since positive pictures have an effect even in the absence of a significant grouping effect, they might represent a grouping factor per se. This was explored in Experiment 3 by removing the connecters.

Experiment 3

Method

Experiment 3 was identical to Experiment 2, with a single modification: the grouping factor "connectedness" was removed. Thus there were only two factors: "type of pictures" (emotional or neutral faces) and "emotion" (congruent positive, congruent negative, or non congruent) resulting in six different conditions with 24 trials for each condition, leading to a total of 144 trials. The analysis of variance was conducted on RTs with two intergroup factors: "type of pictures" and "emotion". A grouping effect was expected to be revealed by varying RTs as a function of the emotion conveyed by the pictures.

Results and discussion

Fifteen students of the University of Strasbourg (8 women, 7 men; mean age 24 years) participated in this study. The mean RT was 838 ms and the mean error rate 3.3%. The analysis of RTs revealed no main effect of the "type of trials" (with emotional vs. with neutral pictures) [(1, 14)=.84, p=.37; η_p^2=.06], and no significant interaction between the "type of trials" and "emotion" (positive congruent, negative congruent, non congruent) [(2, 28)=.45, p=.64; η_p^2=.03] (fig.6). There was no significant effect of error rates either. These results eliminate the possibility of emotion as a grouping factor on its own and suggest an impact of emotion on the organization induced by connecters. However, it still remains to be verified whether a low-level characteristic of the pictures explains the effect rather than their emotional valence. This possibility is explored in Experiment 4 by using inverted faces.

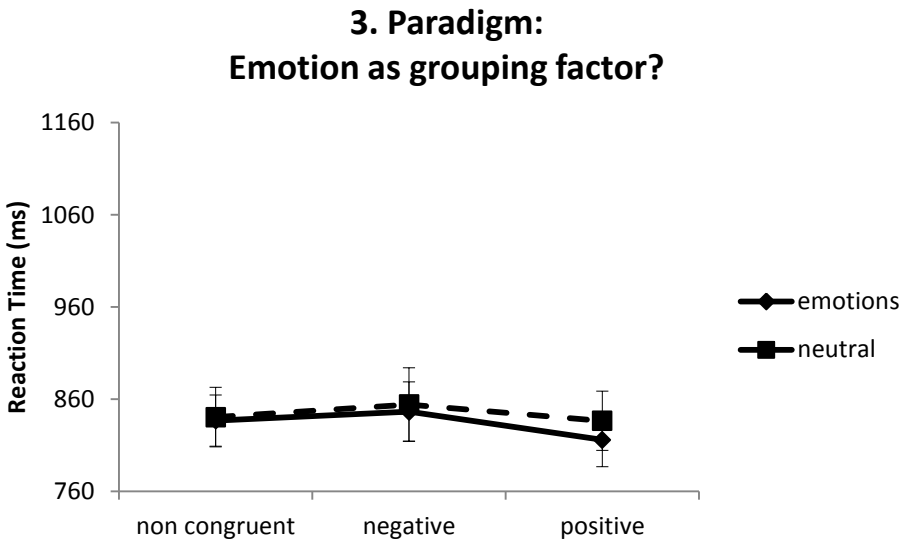

Figure 6. Illustration of the results depicting that emotion is not a grouping factor on its own.
RTs with SEM are averaged over subjects, and represented as a function of the emotional valence of the two pictures that lie behind the targets (on the x-axis; non congruent signifies that the targets are placed on one negative and one positive picture), and of the two conditions "type of trials" (dashed line pictures with emotional valences; continuous line = pictures with a neutral valence). No significant effect could be revealed.

Experiment 4

To check whether our effect was mediated by low-level perceptual characteristics in the faces we created the same paradigm and turned the faces upside down. This experimental manipulation is often used to disentangle the effect of emotion from perceptual effects. Faces are not recognized when they are upside down, and the effect of emotion disappears. However, the low-level perceptual characteristics remain identical. If they are responsible for the effect observed in Experiment 1 and 2, the impact of positive faces should persist when faces are upside down. If the effect is mediated by the emotional valence in contrast, the effect should disappear.

Method

Again the paradigm was identical to the one in Experiment 2, except that faces were upside down. We did not use neutral faces. There were 144 trials with 24 trials for each condition.

Results and discussion

Eleven students of the University of Strasbourg (8 women, 3 men; mean age 23 years) participated in this study. The mean RT was 814 ms and the mean error rate 2.6%. The ANOVA analysis showed an overall effect of connectedness with an advantage for connected targets (connected= 809 ms, unconnected=854 ms; $F(1,10)=6.75$ $p<.05$; $\eta_p^2=.4$]. There was no significant interaction between the grouping factor "connectedness" (targets connected vs. unconnected) and "emotion" (positive congruent, negative congruent, non congruent) [$(2, 20)=.81$, $p=.45$; $\eta_p^2=.07$] (fig. 7) No other effect was detected, and no effect was significant in the analysis on error rates.

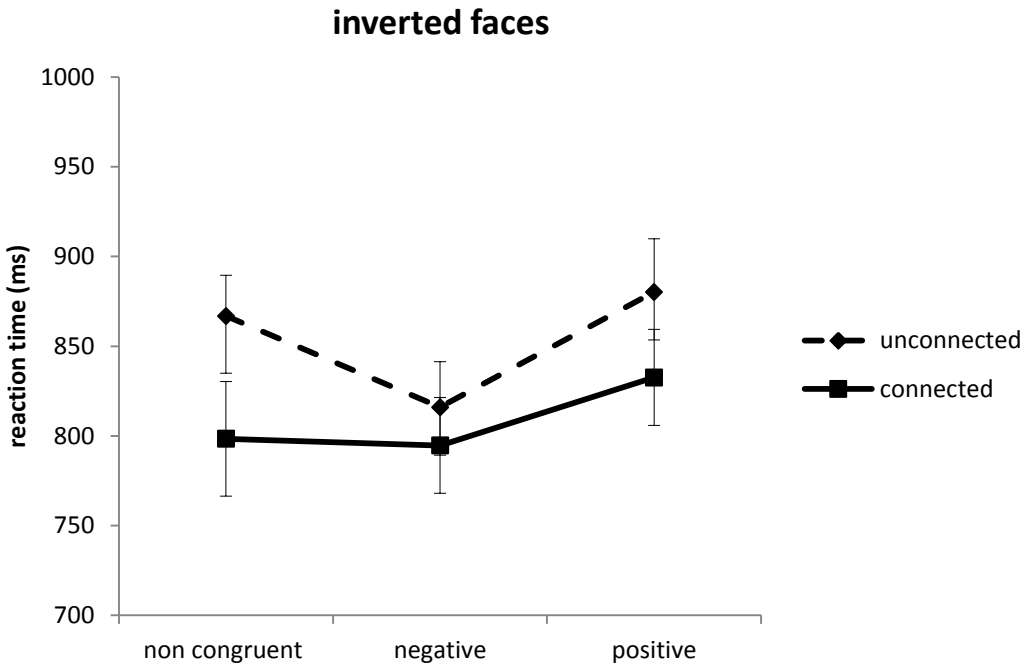

Figure 7. Graph depicting the results in the condition with inverted faces
Mean RTs with SEM, averaged over subjects, as a function of the type of emotion (on the x-axis). The dashed line stands for unconnected targets and the continuous line for connected targets. There was no interaction between the grouping factor connectedness and the factor emotion.

To conclude, there was no effect of positive background faces when they were upside down, suggesting that the effect observed in Experiment 1 and 2 was not due to a low-level perceptual characteristic of these pictures.

Experiment 5

The experiments reported above suggest that positive pictures interfere with the grouping effect by connectors as they reverse the advantage usually provided by the grouping factor in visual search. Experiments 3 and 4 suggest that this effect is not artefactual or due to some low-level characteristics of the pictures. In Experiment 5, our aim was to get at better

understanding of the mechanisms that induce this effect by recording eye movements during the task.

Method

The paradigm was identical to the one in Experiment 2 except that we did not include a condition with neutral faces. There were 144 trials in the session thus 24 trials for each condition. Trials associated with an incorrect response were excluded from the analyses of, RTs and eye movements.

Eye movement recordings and analysis

Right eye movements were measured continuously using an infrared video-based eye tracking system (EyeLink II; SR Research) at 1000 Hz. Before the experimental task, we calibrated the eye tracker by asking participants to repeatedly fixate a 9-point grid. To minimize errors of measurement, participants rested their chin on a chin strap.

Both saccades and fixations were registered and analyzed. Those with a latency of less than 80 ms were discarded as anticipatory. Saccades were defined as having a velocity above 30°/sec or an acceleration above 8000°/sec². They were excluded from the analysis if they were shorter than the size of a single figure. Fixations were only taken into account below 1000 ms. We distinguished saccades and fixations on connected and unconnected distracters, as well as on connected and unconnected targets (fig.8). We excluded the central figure from the analysis, since it belonged to both the target and distractor pair. A

region was thus defined by the figure next to the central one and the region between these two figures.

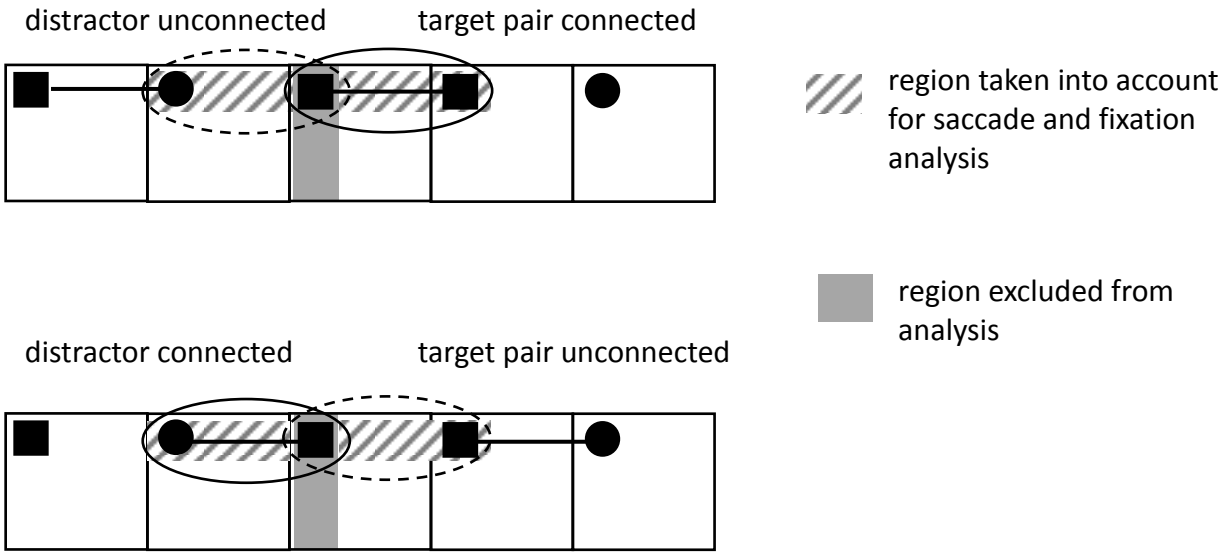

Figure 8. Scan path analyses for the grouping factor connectedness
These graphics illustrate the different zones that we used for saccade and fixation analyses to check for an effect of the grouping factor "connectedness". We compared fixation and saccade duration between the four possible zones which gave us the possibility to see to which amount the connecters and the faces attracted attention.

We also distinguished regions of the figures vs. faces (fig.9). We extracted four parameters: fixation latency (ms), duration (ms), saccade latency (ms), and amplitude (mm). Saccades were considered to be on connected (or unconnected) figures if their end locations were within a pair of connected (or unconnected) figures. We aimed at checking whether the effect of background pictures would be present already at the stage of the initial fixations (latencies) or rather at a later stage of exploration (fixation duration and saccade amplitude).

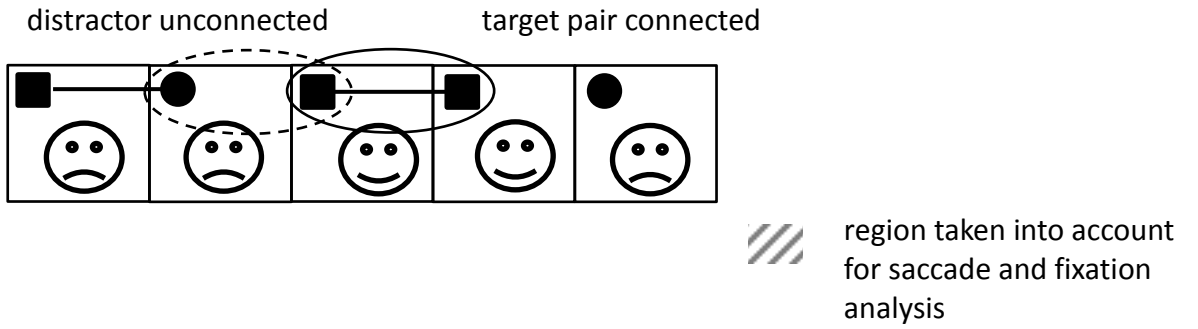

Figure 9. Scan path analyses for the factor emotion
These graphics illustrate the different zones that we used for saccade and fixation analyses.

Results and discussion

Fifteen students of the University of Strasbourg (10 women, 5 men; mean age 23 years) participated in this study, and we were able to record eye movements in 11 among these 15 students. The mean RT was 937 ms and the mean error rate 1.3%. The analysis on RTs revealed a significant effect of "connectedness", with RTs being faster for unconnected than for connected targets (by 75 ms [$F(1, 14)=6.75$, $p<.05$, $\eta_p^2=.32$). There was no significant interaction between "connectedness" (targets connected vs. unconnected) and "emotion" (positive congruent, negative congruent, non congruent) [$F(2, 28)=0.92$, $p=.41$, $\eta_p^2=.06$], but the post-hoc Tukey analysis revealed a disadvantage for connected over unconnected pairs in the congruent positive condition (disadvantage of 103 ms, $p<.05$). The sub-analysis conducted on each "emotion" condition showed a trend towards an advantage for unconnected over connected targets in the condition 'positive faces' [$F(1, 14)=3.96$, $p=.06$, $\eta_p^2=.22$]. There was no significant effect on error rates.

No significant effect was found on fixation or saccade latencies. Total duration of fixations was longer for target than distracter zones [$F(1, 10)=22.7$, $p<.001$, $\eta_p^2=.69$], and

longer for connected targets than unconnected targets zones [$F(1, 10)=8.8$, $p<.01$, $\eta_p^2=.47$]. However, fixation duration did not interact with the condition emotion. The analysis on the total amplitude of saccades on faces (exclusively) showed a significant interaction between the condition 'emotion', 'exploration zone' (target vs. distracter zone) and 'grouping' (targets connected vs. unconnected) [$F(2, 20)=3.9$, $p<.05$, $\eta_p^2=.28$]. We dissected the 3-level interaction by checking the interaction between the factor "connectedness" and the "exploration zone" (target vs. distracter zone) for each condition "emotion" individually. This interaction was significant in the condition positive faces only [$F(1, 10)=5.7$, $p<.05$; $\eta_p^2=.36$]. In this condition, saccades were significantly longer on faces in the target zone when targets were connected rather than unconnected.

All in all, we replicated the effect of Experiment 1 and 2. But most importantly, the scan path evidences a heightened exploration of positive faces when the target pair in the front is connected.

Comparison of Experiments 4 and 5

The presence of a global effect of connectedness in Experiment 4 was intriguing, inasmuch no such effect had been observed in Experiments 2 and 5. On the contrary, there was a slight advantage for unconnected targets in both experiments, either on error rates or on RTs. Since Experiments 4 and 5 differed only on the fact that faces were upside-down in Experiment 4, we compared the results of these two Experiments. Effects that differ between the two experiments can be attributed to the present of upright faces in Experiment 5.

In addition to the usual factors used in the repeated measures ANOVA, we used a between-group factor which was the experiment (4 vs. 5). The analysis showed a significant interaction between the factor "Experiment" and the grouping factor "connectedness" [$F(1, 24)=10.6$, $p<.005$, $\eta_p^2=.31$]. This confirms that the effect of "connectedness" differed significantly in the two Experiments.

Discussion

We replicated a global advantage provided by automatic grouping in Experiment 1 and 4, i.e. subjects being faster at discriminating connected targets in comparison to unconnected targets. This effect was not replicated in the other studies, probably due to the simplicity of the task when the category of the background figures was homogenous. The fact that the advantage provided by automatic grouping was observed again when faces were presented upside-down (Experiment 4) suggests that faces may have a general effect of modulation on the grouping effect. On top of this effect, and despite some discrepancies between experiments, we observed repeatedly that positive faces interfered with the presence of connectors. In Experiments 1, 2 and 5, access to the figures of the target pairs was slower when these figures were connected than when they were unconnected, and this only when they were in front of two positive faces. This effect significantly differed from effects observed with negative or neutral faces (Experiments 1 and 2), suggesting that positive faces interfere with visual organization.

We ruled out alternative interpretations such as the background color or a possible involvement of low-level characteristics of the positive faces. The effect of positive faces disappeared when they were replaced by neutral faces with identical backgrounds

(Experiment 2). It also disappeared when faces were upside down (Experiment 4). Furthermore Experiment 3 showed that the emotional valence of the faces did not represent a grouping factor per se, meaning that the effect of positive faces occurred only in the presence of grouping cues, and more specifically connecters. This suggests that faces interfered during visual organization. To understand how such an interference might occur, let us decompose the different stages that are required to solve the task i.e. to find and identify the pair of identical squares. The first stage corresponds to the automatic grouping of figures. Indeed, the task first requires the examination of the figures in pairs, and preceding experiments have shown a natural prioritization and ocular exploration of connected pairs (Giersch & Rhein, 2008). A prioritization of connected targets during ocular movements was also observed in the present study (Experiment 5). Fixation duration was longer on target than distracter zones, and longer on connected than unconnected regions. This replication of earlier results suggests that connected targets were prioritized like in earlier studies, even in Experiments showing a RT advantage for unconnected targets. It is thus likely that background pictures did not interfere with automatic grouping itself. This is further supported by the fact that eye movements did not show any effect on the latency of the first fixations or saccades. They rather suggested an effect at a later stage of ocular exploration. Indeed, the analysis of ocular saccades showed that the exploration path of positive faces was longer when those faces were located behind connected than behind unconnected targets. These results suggest that positive faces interfere at a stage of form comparison. As a matter of fact, once the figures are organized through automatic grouping, they have to be compared by pairs in order to find the targets. At this stage, subjects should focus on the targets. Hence, exploring the faces distracts from the target comparison. A too long exploration of positive faces could explain a decrement in performance. It is not

enough, though, to explain why the scan path for positive faces is longer for connected than unconnected targets. Connectors are highly visible and help to find the targets, thus they can hardly become detrimental for this task. They can, however, impede the exploration of the faces, by partly occluding them. Connectors thus become detrimental when they are given priority over the targets, i.e. when subjects do not strictly follow instructions. In that case, subjects would engage in organization mechanisms aimed at separating the background face from the connecters in the foreground, which thus slows down the comparison of the targets. It has indeed often been described that background/foreground segmentation is a time-consuming process (Guttman, Sekuler, & Kellman, 2003). Conversely, the exploration of positive faces may attract attention and thus guide visual exploration towards unconnected targets, in which case there is no need to engage in segmentation processes to separate the targets from the background faces. The latter effect would explain the negative correlation between RTs for unconnected targets and the evaluation of the positive valence of the faces in Experiments 1 and 2.

All in all the results point towards an automatic attraction of the positive faces, which impaired the performance when the target pair was connected and facilitated the performance when there was no connecter. Since our task is a visual search task, these results may appear at odds with the face-in-the-crowd effect. It is widely reported that angry faces are found more quickly (see Shasteen et al. 2014, for a recent study), although this conclusion has been questioned (Becker et al., 2001). Regardless, the differences in methodologies between the typical visual search paradigm and our study lead to the conclusion that we are not observing the same type of interference. The paradigms that have been used for the face in the crowd effect, usually explore the propensity of the subjects to direct their initial attention towards faces. Such an effect on saccades or fixation

latencies was not observed here, possibly due to the fact that background faces played an incidental role in the task (Barratt & Bundesen, 2012; Stein et al., 2009). The interference of the faces occurred at a later stage during form comparison, as suggested by the eye movement analysis. So, why do our positive faces have such a distracting effect? It is unlikely an effect of alert, since the positive faces were rated as less arousing than the negative faces. It is important to note that these faces were different from the usual happy faces used in the literature to explore attention capture, and this difference might represent an explanation for our effects. Here, the positive emotional valence of these faces was not related to the expression of the faces. They did not include an open mouth or other highly contrasting characteristics, and only one was slightly smiling. The effect we observed is thus most likely due to the fact that positive faces were nice and attractive. As a matter of fact, when we asked subjects to rate the attractiveness of the faces, positive faces were rated as clearly more attractive than negative faces (positive= 5.8 (1.1); negative=3.5 (0.9) $F(1,14)=41.6$, $p<.001$; $\eta_p^2=.74$). This factor might be important to take into account in future studies exploring the influence of emotional faces on visual processing.

All in all, it is the saliency of the background information that disturbs visual organization. Faces globally reduce the advantage provided by grouping, by distracting subjects from the connected targets. The subjects' attention is drawn to the faces, and they explore the salient rather than the target information. This requires time-consuming background-foreground segmentation when the connecter occludes the salient faces, and an acceleration of the target detection when no segmentation is required. This effect is especially marked in case of positive faces, which systematically induced a reversal of the usual effect of grouping by connectedness. It is a question for future studies if the results

observed in the present study would persist in case of grouping without physical connecters, e.g. grouping by color.

Yet, the important point of this study is that positive faces affect the way we explore and access visual information. This might represent a way to adapt our exploration to the saliency of information and to our needs.

Acknowledgments

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Chapter 3:

Do positive faces distract patients with schizophrenia as well?

Introduction

As described above, we created a paradigm that demonstrates how positive faces, which are incidental for the very simple grouping task, distract the subject to such an extent that their performance is disrupted during visual organization. These results emphasize the importance of positive faces, which the participants did not manage to ignore. Processing and understanding the emotion conveyed by a facial expression is important as it represents a capacity for nonverbal communication (Kohler et al., 2010). With the application of our paradigm in schizophrenia, we hoped we would be able to shed light on more implicit aspects of facial expression recognition in patients.

If the results for patients with schizophrenia are the same as for control subjects, then they would show that emotional processing is preserved at least partially in patients. In contrast, if the results are different between groups, this could give a first idea of how patients' perception is altered by emotional information.

Material and Method

23 patients and 23 healthy control subjects (6 women, 17 men in each group) were included in this study. More detailed demographic information about the two groups can be found in table 4.

	PATIENTS	CONTROLS
Gender (**M/F**)	17/6	17/6
Age (**mean ± SD**)	36.8 ± 9.3	36 ± 10.6
Years of education (**mean ± SD**)	13.3 ± 2.2	13.3 ± 2.3
Medication (**typical/atypical/no medication**)	6/15/2	—
Dose of chlorpromazine equivalents	235 mg/day	—
Anti-parkinsonian treatment (tropatepine)	3	
Mean Disease duration (years)	12 ± 7.6	
Outpatients/Inpatients	22/1	
PANSS positive symptoms (**mean ± SD**)	17.8 ± 5.8	—
PANSS negative symptoms (**mean ± SD**)	21.9 ± 7.8	—
PANSS general symptoms (**mean ± SD**)	38.6 ± 10.4	—
PANSS total (**mean ± SD**)	**77.0 ± 19.3**	—

Table 4. Demographic information about patients and healthy controls.

Stimuli

The stimuli were the same as used in the previous experiments based on the repetition discrimination task. For this study we used the paradigm with emotional faces in two conditions. The first condition 'emotion' was based on the use of faces with emotional valences, and the second condition 'neutral' on the use of faces with a neutral valence. The two conditions were applied in one paradigm and were subdivided in the same way as described earlier. In the emotion condition there were three different possible background dispositions, based on the emotional contents ('congruent positive' vs. 'congruent negative' vs. 'non congruent') and two connectedness conditions (within-group vs. between-group

pairs). In the neutral condition the subdivision was the same way based on the background colors used in the emotional condition. Thus altogether this resulted in 12 different conditions (table.5).

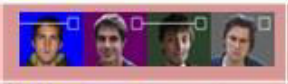
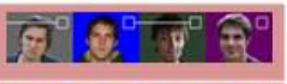
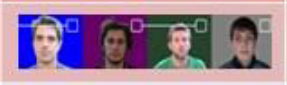
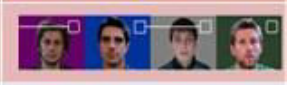
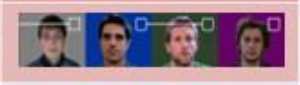
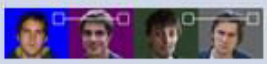
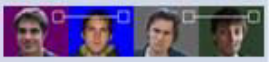
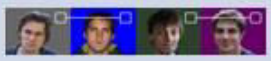
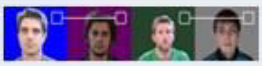
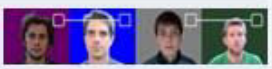
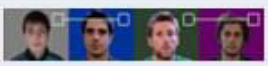
12 Conditions	Stimuli	A positive congruent	B negative congruent	C non congruent
1 target pairs connected	emotional			
	neutral			
2 target pairs unconnected	emotional			
	neutral			

Table 5. Table representing the twelve conditions used in this paradigm.

The training consisted of 16 practice trials directly followed by 288 proper trials composed of 144 trials for each global condition (emotion vs. neutral pictures presented in random order). The 6 pictures, the shapes (squares with sharp and rounded edges) and their location, the conditions (‘connected pairs’ vs. ‘unconnected pairs’, ‘congruent positive’, ‘congruent negative’, or ‘non congruent’) were equally represented. The order of the trials was randomized.

Procedure

The procedure was the same as in the previous experiments. Each subject completed the whole study and evaluated the valence and arousal levels of the pictures with the SAM, after completion of the task.

Results and discussion

We analyzed the results with a repeated measure ANOVA, in order to compare differences in the two groups as a function of the two conditions and the respective sub conditions.

There was no global interaction between the factor “group” (patients vs. healthy controls), the factor “connectedness” (targets connected vs. unconnected), types of pictures (emotional vs. neutral faces) and the factor “emotion” (non congruent vs. positive congruent vs. negative congruent) ($F(2,88)=.23$; $p=.79$). Furthermore there was no interaction between the factor “group”, the factor “connectedness” and the factor “emotion”, when we dissected the results and analyzed each of the two global conditions emotion and neutral pictures individually (emotion: $F(2,88)=1.24$; $p=.3$; neutral: $F(2,88)=.8$; $p=.45$). However there was an effect of the factor “emotion”, independent of the group.

The global analysis revealed a significant interaction between the factors ‘connectedness’ (connected vs. unconnected targets), the factor ‘type of pictures’ (emotional vs. neutral faces) and the factor ‘emotion’ (non congruent vs. positive congruent vs. negative congruent) ($F(2, 88)=3.4$; $p<.05$; $\eta_p^2=.07$) (fig 14). This enabled us to further dissect the analysis.

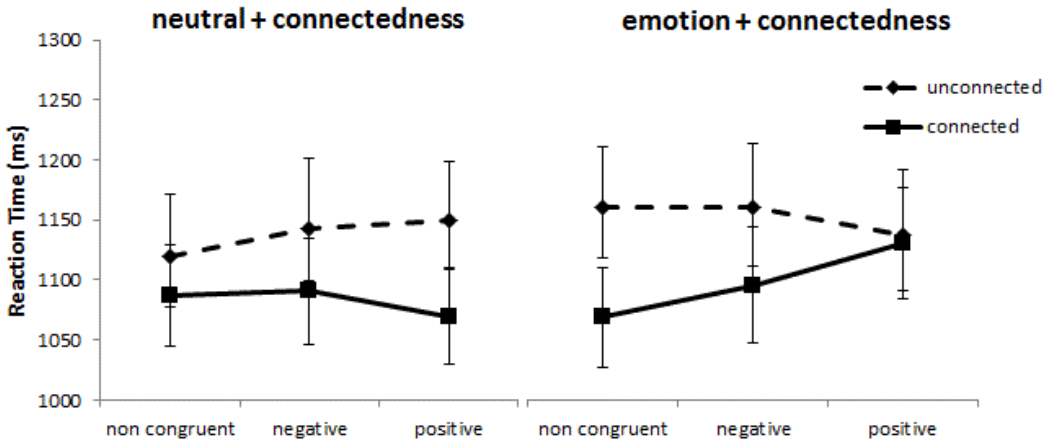


Figure 14. Illustrations of the response times as a function of the two main conditions (emotional faces vs. neutral faces). No group differences were detected, thus these results represent the combined mean response times of patients and healthy controls. In each panel RTs are displayed as a function of the presence of connectors relating the geometrical target figures (plain line for connected vs. dashed line for unconnected targets), and of the emotional valence of the background pictures (non congruent, congruent negative and congruent positive from left to right). In the neutral condition, faces were not emotional, but the background colors of the faces corresponded to those of emotional faces.

We therefore conducted ANOVAs to compare performance with emotional vs. neutral faces for each background condition (non congruent, congruent positive and congruent negative). This analysis revealed a significant interaction between the factor "connectedness" and the type of pictures (neutral vs. emotional faces) in the background condition with positive congruent faces ($F(1,45)=4.69$, $p<.05$; $\eta_p^2=.09$), no interaction in the background condition with negative congruent faces ($F(1, 45)=,12$, $p=.73$) and a tendency for the condition with non-congruent faces ($F(1, 45)=4.04$, $p=.05$). Hence, again we find a distracting effect of positive faces. Moreover, this effect is the same for patients with schizophrenia and healthy control subjects.

Regarding the agreed impairment of face recognition processing in patients in the literature, this effect might seem surprising at first sight. However, our task differs from the

literature on several points. First it does not require direct judgment on the facial expression which could be a first explanation of the discrepancy between our results and the literature.

Another point that differentiates our paradigm from the ones cited in the meta analysis by Kohler et al., 2010, is the choice of pictures. We used stimuli taken from the IAPS which are evaluated on valence and arousal levels. However the expression on the faces may not be the crucial factor. We chose negative pictures which resemble angry faces. However the positive faces are not overtly expressive but rather convey a positive impression. Each subject rated valence and arousal levels after the experiment and we compared the ratings between patients and healthy control subjects. There was no difference between groups on positive faces. This gives some indication on how such positive faces are processed by patients. The faces in our task play an incidental role and the most efficient strategy for the subjects should have been to ignore these pictures. However this is not what happens, the positive faces distract the subjects from the task and thus alter the results. If patients face recognition impairments were due to early visual processing mechanisms, and an inability to detect facial expressions, we should have seen no effect of these faces on the task. The difference with the literature (e.g. Loughland et al., 2002) might be due to the differences in the paradigms, and in particular to the fact that faces played an incidental role in our test.

Our results rather suggest an effect at the level of subjective evaluation which is further supported by the subjective evaluation on negative and neutral faces. There was no difference in valence ratings, but patients rated neutral as well as negative pictures as more arousing (table 6). Increased arousal rates have already been described in patients with schizophrenia (Lakis & Mendrek, 2013), though these differences did not seem to affect the results in our task. This effect on arousal evaluation might be another point in favor for the

hypothesis that it is rather the conscious interpretation of the pictures that is impaired in patients. In contrast, their attention is automatically drawn to positive pictures in the same way as for healthy controls.

VALENCE	Patients	Healthy controls	t-test
Neutral	5.29 (1.1)	5.31 (0.7)	t= -.08 p=.94
Positive	6.12 (1.5)	5.92 (0.9)	t= .58 p=.57
Negative	3.65 (1.7)	4.03 (1.3)	t= -.83 p=.41

AROUSAL	Patients	Healthy controls	t-test
Neutral	3.55 (1.5)	2.06 (1.5)	t= 2.04 p<.05
Positive	3.5 (1.7)	2.7 (1.7)	t= 1.55 p=.13
Negative	5.0 (2.3)	3.37 (2.1)	t= 2.45 p<.05

Table 6. Subjective valence and arousal ratings of the used stimuli. There are no differences in valence ratings between patients and healthy controls, however patients rated arousal levels of neutral as well as negative faces significantly higher than healthy controls.

All in all, these results suggest that positive faces have a great salience even for patients. However there are several limits to these results. First, we cannot affirm that patients have preserved emotion categorization. Our stimuli are not adapted to this question, and only give partial indications, on the processing of positive faces. Moreover, it can also be questioned whether this effect would generalize to other types of pictures. Given the fact that faces have to be considered as special stimuli, due to their social role, further studies should include emotional stimuli from different categories.

Chapter 4: Discussion

To summarize, we have developed a new paradigm that can measure the impact of emotional stimuli during automatic visual grouping. The fact that stimuli conveying emotional information have an impact on cognition is widely accepted today. However, cognition as well as emotion are two umbrella terms that comprise multiple mechanisms with different functions. The interaction between emotion and cognition thus varies according to the specific mechanisms and stimuli involved in a given task or situation. Here we concentrated on the impact of emotional stimuli on visual perception. We provide a paradigm for which the emotional stimuli are interchangeable, which makes it possible to compare the impact of different stimuli categories and valences.

Our results provide evidence for a distracting effect of positive faces and negative animals during visual grouping. This effect was not found for negative faces, positive animals or stimuli from the other categories which contained social scenes and objects. Visual grouping through connectedness has been shown to attract attention as have emotional stimuli. Here we show that when in competition with these visual grouping stimuli, positive faces are given priority. With the additional control experiments, we are confident that an effect of low level characteristics cannot account for these results. Indeed, both the use of neutral faces and of inverted faces nullified the effect of emotional faces.

4.1. Positive faces are complex stimuli: happy or likable?

The literature on the recognition of facial expressions is vast, and since a recent review insists on the strong effect of positive faces (Becker et al., 2011), our results seemed congruent with at least part of the literature dealing with the interaction between emotion

and perception. We were thus tempted to compare our results to the ones in the literature. A large variety of faces has been tested and the stimuli range from real pictures to schematic pictures, in which low level characteristics are controlled for (open mouth/teeth…) (review Becker et al., 2011). Despite this large choice, we have realized that we cannot really compare our stimuli to those that have been used previously. Indeed to the best of our knowledge, these stimuli all express explicit emotion, i.e. the positive faces are all smiling. In contrast, the positive faces we used, did not express a direct emotion, but their positivity was rather due to some other characteristic. They were nice to look at, which is why our first guess was that they are more attractive. Indeed ratings showed that the positive faces were rated as more attractive than negative faces. This could however be a biased measure, as facial expression can influence the judgment of attractiveness (Golle, Mast, & Lobmaier, 2014), and we could not measure the attractiveness of the neutral faces. Hence, other terms might be more suitable to describe why theses faces are rated as positive. Further studies are needed to elucidate this question. Faces might also be likable, friendly or trustworthy. It would be interesting to add these measures in order to go further in the interpretation of our results. In fact attractive and trustworthy faces have been shown to activate the reward circuitry (Bzdok et al., 2011). Maybe these faces incite exploration because they invite for social interaction? Interaction could be seen as a social reward.

It is to be noted, however, that an explanation in terms of social reward would make it all the more surprising that the effect of positive faces is preserved in patients, who generally have a poor social life and difficulties to interact with other people. This question is further explored in the next paragraph

4.2. Preserved effect in patients

We have replicated our results several times and were able to test the paradigm in patients with schizophrenia. No matter why exactly these faces are this important and disturb even a very easy cognitive task for visual organization, this task is a good mean to compare the impact of emotion between patients with schizophrenia and healthy control subjects.

Though patients have often been described as impaired in the discrimination of emotional facial expressions (Campanella, Montedoro, Streel, Verbanck, & Rosier, 2006; Daros, Ruocco, Reilly, Harris, & Sweeney, 2014; Turetsky et al., 2007), these emotional faces used here, have the same distracting effect on patients as on healthy controls. We have suggested that the difference with the literature might be due to the incidental influence of faces in our paradigm, in contrast with more explicit tasks in the literature. In fact, patients did rate neutral faces as more arousing than healthy controls, which corroborates the difficulties described in the literature. Here however neutral stimuli are evaluated as being more arousing but they do not attract patients' attention more than controls. This result is surprising, but confirms that the distractive effect of positive faces is not due to a trivial arousal effect, but rather to some other characteristic.

Further studies are necessary to confirm our results, especially in patients. Different stimuli should be used, such as different faces with other expressions, or maybe the same faces that evoke positive and negative emotions. Also the use of eye tracking could give more insight, and show whether patients and healthy control subjects are really attracted in the same way towards positive faces. We discuss the perspectives of this work in more detail in the general discussion. As a matter of fact, further data on emotion processing in patients was also collected in our last study on pain perception.

Part 3

second study

Pain and emotion perception in patients with schizophrenia

Chapter 1: Introduction

In parallel to the first study, where we were mainly interested in visual perception, we conducted a second study dealing with a different kind of perception, which seems also altered in patients with schizophrenia: the perception of pain. I will give a short overview of pain perception in general and pain perception in patients in order to introduce our study.

1.1. Pain perception

Pain perception is an important part of somatosensation, which protects the body from possible physical harm and informs about internal injuries or dysfunctions that cannot be seen with the naked eye.

Pain has been defined by the International Association for the study of pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. This definition implies that pain perception is composed of different components. These can be summarized as a physiological, sensory/affective and a cognitive component, which we will briefly describe in the following section. Here again we will not be exhaustive, since our objective is not to study the mechanisms of pain, but to establish to which amount pain perception is altered in patients.

1.1.1. Physiology and anatomy of pain perception

Like each form of perception, pain perception starts at the sites of specialized receptors. For pain, these receptors are called nociceptors and they respond to tissue damage, intensive pressure or high intensity mechanical, thermal or chemical stimuli. They are mostly free

nerve endings that are located in the skin, joints and the outer layers of viscera. They are attached to myelinated Aδ and unmyelinated C fibers which conduct the information in form of an electrical signal to the dorsal horn of the spinal cord. Myelination serves as an accelerator thus Aδ fibers transmit the information more rapidly than C fibers. The first neuron that transmits the noxious stimulus from the nerve ending to the dorsal horn is called first order afferent neuron, and transmits the signal via an interneuron to the second order afferent neuron. These second order neurons are called relay neurons, because they transmit the information to the thalamus which is considered as the relay station. Neurotransmitters involved in the transmission of nociceptive information are excitatory (Glutamate and Substance P) or inhibitory (GABA). The neurotransmitters released by the first order neurons can thus activate the interneurons which in turn activate the second order neurons.

The dorsal horn of the spinal cord is separated in different layers. The information can be sent directly to a motor neuron which will trigger a motor reaction known as reflex. Else, the information is redirected to different parts of the thalamus, depending on the location and the type of stimulus. The thalamus then serves as a relay station and transmits the information to different cortical and subcortical areas of the cerebral cortex, such as the somatosensory cortex, the insula and the anterior cingulate cortex, where the stimulus' valence can be evaluated.

There are several kinds of responses that a painful stimulus can trigger, physiological as well as behavioral. Pain often triggers the elevation of autonomic nervous system activities, such as the increase of heart rate and galvanic skin response (Kyle & McNeil, 2014), which prepare the body to be aware and react rapidly to stimuli that are dangerous.

Pain perception and evaluation is thus necessary in order to stay alive and react to the cause of the noxious stimuli as soon as possible. Usually the feed forward sensory processing of pain is considered as innate, but living in a social environment teaches us how to react and interpret our perception (Cervero, 2012).

Additionally to these different ascending pathways, there are descending pathways (fig.15) which can regulate nociception by releasing neurotransmitters that can facilitate or inhibit the initial signal. Melzack and Wall have proposed the gate control theory in 1965 which states, that the substantia gelatinosa of the dorsal horn gates the perception of pain by integrating the incoming information from the first order afferent neurons and downstream information from the brain (Melzack & Wall, 1965).

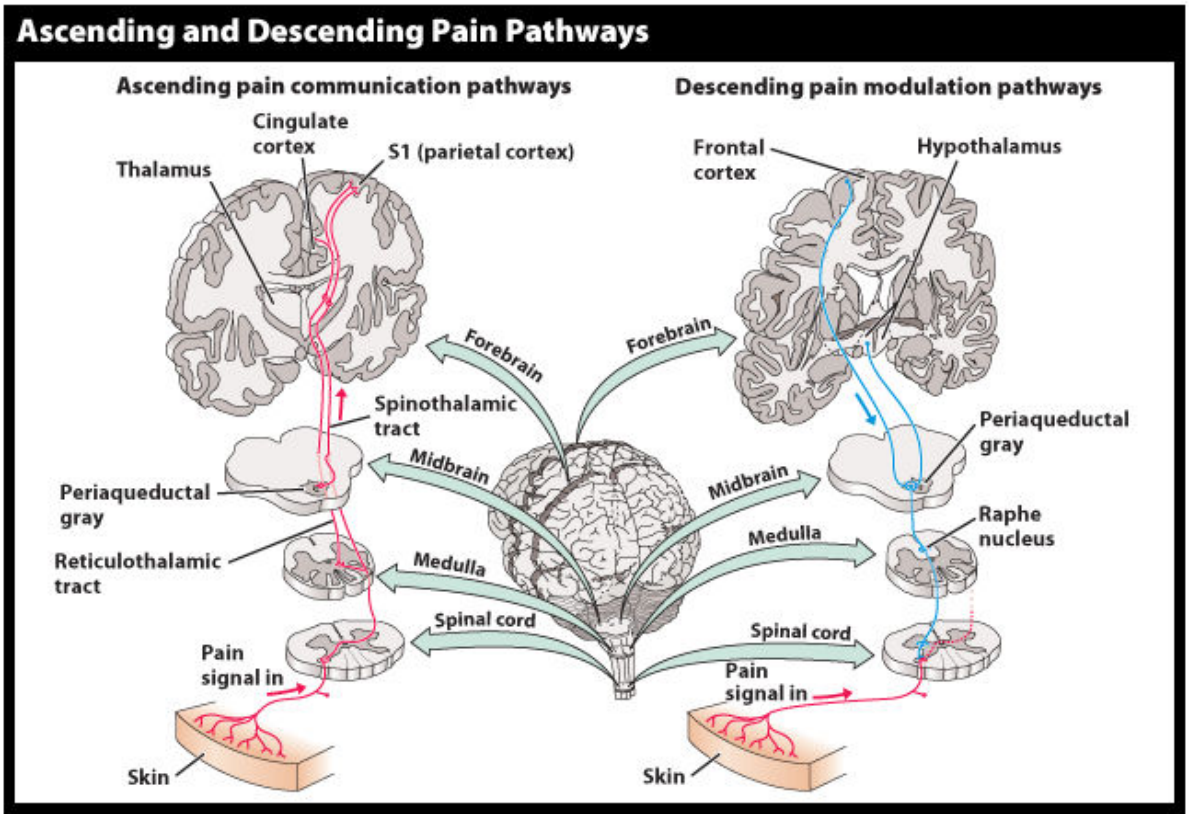


Figure 15. Ascending and descending pathways of pain perception, taken from http://www.biopsychology.com/6e/activity0805.html.

1.1.2. Cognitive, Affective and Behavioral Processes

Considering the importance of the top down pathways that we have described, it becomes plausible that cognitive components are involved in pain perception and that they might even alter the sensation of pain.

There are two major cognitive processes that have to be considered in pain perception and which play an important role: attention and anticipation. Attentional distractions are frequently used for children when they have to get an injection for example. They reduce pain related activations in several pain related brain areas as for example somatosensory cortices and the thalamus (Bushnell, Ceko, & Low, 2013; Tracey & Mantyh, 2007; Villemure & Bushnell, 2002). Anticipation of a stimulus can also alter cortical systems involved in pain processing (Porro et al., 2002; Sawamoto et al., 2000) and it has been shown recently that this alteration is correlated to the expectancy of the intensity of the stimulus. If the participant expects the stimulus to be painful, the anticipation can increase the painfulness of the stimuli. In contrast, if the stimulus is expected to be harmless, the painfulness is lower. Importantly these opposite effects occur with identical painful stimulations (Goffaux, Redmond, Rainville, & Marchand, 2007).

Conscious pain perception is further complicated by the fact that it is evaluated along different dimensions, i.e. as painful, dangerous and negative. This evaluation is very important, since it is necessary to adapt behavior, like e.g. seeking help or protecting the body from further harm. However there are situations in which pain is not the sole alert stimuli anymore but persist even though the danger is withdrawn, taken care of, or even absent. Thus a psychological component comes into play which helps to deal with this kind of pain but also pain in general. Thus pain has to be evaluated as bearable or unbearable,

transitional or even unfair. This kind of evaluation plays a great role in the well-being of people that suffer from chronic pain for example. If a person is under the impression that there is nothing that can stop this pain, the negative feelings can even lead to depression (Garland, 2012)

Since pain perception is multimodal and requires the correct functioning of several actors, there are multiple diseases related or correlated to a dysfunction of pain. Only to name some of them, there is chronic pain, phantom limb pain, Lesch-Nyhan syndrome, and even a gene mutation that creates a total absence of pain. Some of these diseases are genetic, others physiological and yet others are mental diseases. One of the mental diseases that have often been linked to an absence of pain perception is schizophrenia. In the following section, we summarize evidence for alterations in pain perception in schizophrenia.

1.2. Pain Perception in Schizophrenia

Despite the potential importance of a decrease in pain sensitivity in patients with schizophrenia, this symptom has only rarely been studied experimentally. Without knowing the mechanisms of this insensitivity to pain, it is difficult to evaluate the patients' grievance to pain. Clinical descriptions of auto-mutilations and insensitivity to pain, especially during surgery, are very common in the literature (review in Dworkin 1994), but experimental data have disclosed various discordant results (review in Bonnot, Anderson, Cohen, Willer, & Tordjman, 2009; Singh, Giles, & Nasrallah, 2006). There are different possibilities that might explain the heterogeneity of these results. First of all there are several differences as to the choice of population and experimental design, which make it difficult to compare the results

without reservation. We tried to give an almost exhaustive overview of the experimental studies with their differences in Table 7. We display the different kinds of pain inductions as well as the clinical states that the patients were in at the time of the respective studies. To be more specific, there are studies that tested pain perception in patients in an acute phase, unmedicated patients, hospitalized patients or stable patients. The different means of pain induction ranged from electrical to thermal and mechanical stimulations with a variety of measures. Pain perception was measured with subjective rating scales or with electromyocardic, autonomic response recordings (review in Potvin & Marchand, 2008), and once with electroencephalographic recordings (Davis, Buchsbaum, van Kammen, & Bunney Jr., 1979).

Due to these differences it is complicated to conclude, whether patients are less sensitive to pain or not and to make assumptions about the subtending causes. Until now there is one meta-analysis which calculated a moderate effect size suggesting a diminished pain response in patients with schizophrenia (medicated as well as non-medicated). However, the authors of the meta-analysis could only include 12 comparable studies (Potvin & Marchand 2008). The contrast between the number of experimental studies conducted, and the clinical importance of this disorder leads us to concede a particular importance to this question.

We reasoned that a better understanding of pain perception in patients requires to distinguish different aspects involved in pain. First there is an ambiguity in the literature due to mostly subjective measurements of pain perception, which makes it difficult to conclude whether the insensitivity that has been found, is the result of a lack of expression or

impaired nociceptive[3] processing. A lack of expression would mean that patients do feel the pain but won't complain about it. A decreased pain evaluation might be due to a difficulty in patients to express themselves in a clear and coherent way. We needed to bypass the verbal responses to pain, and thus used an 'objective' measure, i.e. EEG. It is to be noted that by 'objective measures', we do not mean responses without a subjective component, but a response that does not necessitate a verbal or behavioural response. Even if EEG measurements may capture a signal related to the subjective experience of pain, they still bypass the verbal expression of pain, and in this sense provide a more objective measure than the verbal report. Only a sparse number of studies have evaluated pain perception in an objective manner in patients, and here we employed EEG measurements. For the rare studies who did include such an 'objective' measure, all used different kinds of measurements, like, the measure of nociceptive reflex (Guieu et al 1994), the autonomic response (Goldman et al 2007) EEG recordings (Davis et al 1979), and fMRI (Fuente-Sandoval, Favila, Gómez-Martín, León-Ortiz, & Graff-Guerrero, 2012). Though the nociceptive reflex was normal, the autonomic response as well as the evoked potentials caused by nociceptive stimulation, were decreased in patients. Complementary studies are necessary to enlarge and confirm these results. The study we present will answer to this need by means of ERP recordings. Besides we also tested different components of pain perception, and in particular the role of emotion and attention. These components can both influence the perception of pain but have not been explored in this framework in patients with schizophrenia (Dworkin 1994 ; Potvin et al 2008). In order to go a bit farther, we also explored the neurobiological foundation of pain perception in patients. We verified in which way the threshold of pain perception is linked to the activity of (1) the dopaminergic

[3] Nociception= the neural processes of encoding and processing noxious stimuli (Loeser & Treede, 2008)

pathway (homovanillic) and (2) the secretion of substances when the adrenocorticotropic axis is activated (cortisol, ACTH, adrenalin and its catabolit vanillylmandelic acid). Here we chose to focus on these two pathways because they are both important in processing of nociceptive information, and have been shown to be altered in schizophrenia. (1) The dopaminergic system has been shown to be hyper activated in patients with schizophrenia in the mesocortical area which is linked to reward processing. In nociceptive information processing the dopaminergic receptor D2 seems to be implicated in the diffuse noxious inhibitory control mechanism (Guillin, Abi-Dargham, & Laruelle, 2007; Laruelle & Abi-Dargham, 1999; Potvin, Grignon, & Marchand, 2009). (2) Nociceptive stimulation induces stress, and this stress comes along with the activation of the adrenocorticotropic axis (Mensah-Nyagan, Meyer, Schaeffer, Kibaly, & Patte-Mensah, 2009). An abnormal sensitivity for stress has been observed in patients, with increased plasma ACTH levels (Brunelin et al., 2008).

Our main 'objective' measure, however, consisted in EEG recordings, and the principles of this measure are presented in the following chapter.

authors	patients/ controls	state	type of pain	measure	Conclusion (effet in patients compared to controls)
May 1948	343/100		painful pinch	pupillary dilation	diminished pupillary dilatation
Earle and Earle 1955	36/15		cold pressor	blood pressure	decreased blood pressure response
Collins and Stone 1966	18/56	no medication/inpatients	electrical stimuli	pain/sensory threshold Pain tolerance	increased sensation threshold, no difference in pain threshold or tolerance
Ax et al. 1970	28/18	off-medication	electrical stimuli	conditioning, skin conductance/ blood pressure	higher skin conductance/no difference in blood pressure/ no difference in response to conditioning
Kane et al. 1971	30/15	chronic inpatients	thermal stimuli	verbal reports on pain tolerance, warmth detection and pain detection threshold+ pupillary dilation	chronic patients are less sensitive to noxious stimuli the other measures differed between groups of patients that were not clearly defined
Davis et al. 1979	17/17	off-medication	electrical stimuli	EEG/pain tolerance	lower somatosensory evoked potential, no difference in pain tolerance
Dworkin et al. 1992	13/19	inpatients	thermal stimuli	Pain discrimination and response	poorer sensory discrimination, no difference in pain tolerance

authors	patients/ controls	state	type of pain	measure	Conclusion (effet in patients compared to controls)
Dworkin et al. 1992	13/32	inpatients	thermal stimuli	Pain discrimination and response	poorer sensory discrimination, no difference in pain tolerance
Guieu 1994	10/10	off medication	electrical stimuli	leg flexion reflex/ electromyography recording + statement when painful	no difference in reflex and subjective thresholds
Kudoh 2000	50/25		electrical stimuli	pain threshold	increased perception thresholds and less post-operative pain
Song et al. 2000	21/23	acute	mechanic	pain pressure threshold	pain insensitivity correlated with acute positive symptoms, decreased symptoms = decreased pain insensitivity
Blumensohn et al. 2002	25/29	stable/no benzodiazepines/ inpatients	electrical stimuli	pain/sensory threshold pain tolerance	increased sensation threshold, pain threshold and pain tolerance but no difference in VAS ratings

authors	patients/ controls	state	type of pain	measure	conclusion(effet in patients compared to controls)
Jochum et al. 2006	23/23/23	inpatients: acute no medication vs. Acute with neuroleptics	thermal stimuli	press stop button when warmth or pain is felt	increased latency for warmth detection and higher heat pain threshold then controls/ no effect of antipsychotics on pain perception
Atik et al. 2007	27/59 schizo/30 bipolar	outpatients/medicated	thermal stimuli cold pressor test	threshold/endurance/VAS for pain intensity	patients higher pain threshold than bipolar patients/no diff to controls/higher pain endurance than controls
Goldman et al. 2007	24/12	mixed	thermal stimuli cold pressor test	Blood samples (5HPA axis) /likert scale/pain tolerance/blood pressure	subjective responses to pain no difference/ but tested three different groups
Potvin et al. 2007	23/29	mixed	heat pulse/cold pressor test	VAS/ DNIC/ temporal summation	normal processing of acute pain/ lack of pain sensitization
Fuente-Sandoval et al. 2010	12/13	unmedicated	thermal	subjective ratings of pain intensity/ unpleasantness + fMRI	no difference in pain tolerance or subjective ratings, but higher activation in primary somatosensory cortex/less activation in Insula, PCC, brainstem

authors	patients/ controls	state	type of pain	measure	Conclusion (effect in patients compared to controls)
Girard et al. 2011	35/35	stabilized	ischemic and pressure pain	VAS+ Heart Rate	more sensitive to pressure and ischemic pain/ no difference of heart rate
Fuente-Sandoval et al. 2012	12/13	treated stable	thermal	subjective ratings of pain intensity/ unpleasantness + fMRI	no difference in pain tolerance or subjective ratings, but higher activation in primary somatosensory cortex and superior prefrontal cortex/less activation in posterior cingulate cortex and brainstem
Levèsque et al. 2012	12/13	treated	painful sural nerve stimulation	pain and reflex threshold/ verbal numerical rating scale	increased sensitivity to acute pain (lower pain detection threshold), decreased pain sensitization
Boettger et al. 2013	18/18	unmedicated acute	cold and heat pain	cold and heat pain thresholds (stop button) + VAS intensity and unpleasantness/thermal grill illusion	higher heat and cold pain thresholds/ no difference in unpleasantness/ no difference in temperature difference of grill illusion

Table 7. Table of experimental studies that have been conducted on the behalf of pain perception in patients with schizophrenia. We included only experimental designs that included a group of healthy control subjects.

1.3. Brain activity recordings with electroencephalography (EEG)

With the EEG method we recorded brain activity throughout the whole experiment. To that aim, we applied 64 electrodes on the head of each subject, using the 10/20 system developed by H.H. Jasper (Klem, Lüders, Jasper, & Elger, 1999). This reference system divides the scalp into areas that represent about 10 to 20% of the scalp (fig.16; fig.17). The data recorded represents the by voltage changes of the millions of neurons that form our brain. These voltage changes are created by the emission of neurotransmitters into the synapse and their fixation on their receptors. This can provoke the opening of ion channels which results in a voltage change. This voltage change can in turn induce an 'action potential'. Since the voltages are very low, ranging from less than a microvolt to several microvolts, the signal that is measured during EEG is the outcome of the activation of multiple neurons and has to be amplified.

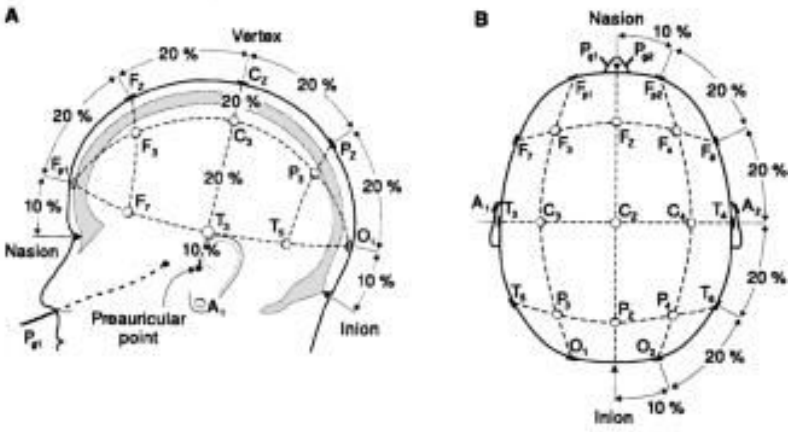


Figure 16. The disposition of electrodes according to the 10/20 system proposed by Jasper (taken from http://theses.univlyon2.fr/documents/getpart.php?id=lyon2.2002.fort_a&part=5783).

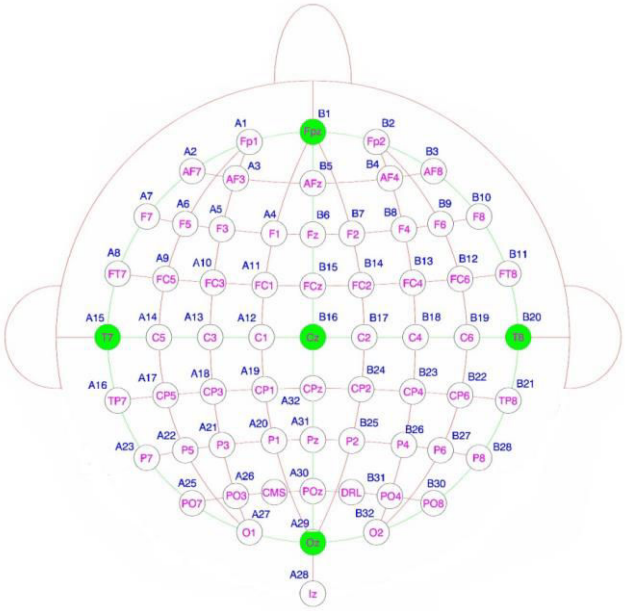


Figure 17. Here, all the 64 electrodes we used are presented in their respective location The image was taken from http://www.biosemi.com/ headcap.htm

The signal is registered continuously during the tasks, and we used a digital system to send triggers (i.e. to mark a certain point in the EEG data file) that indicated the moments of the different phases of the experiment, like e.g. the onset of a stimulus.

Different artifacts can make the results noisy, like the eye movements and electrical voltages coming from the environment. These signals are measured and excluded. To that aim we applied 2 additional electrodes on the earlobe. They represent the reference electrodes because the data recorded at these sides remains stable. In order to measure vertical as well as horizontal eye movements we applied 4 electrodes around the eyes and subtracted these eye movement artefacts from the final analyses. This allowed us to clean our recordings from artefacts that resulted from eye movements and other electrical voltages from the environment.

Chapter 2:

Neurophysiological evidence for enhanced pain sensitivity in patients with schizophrenia.

Neurophysiological evidence of enhanced pain sensitivity in patients with schizophrenia

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Abstract

Background: Patients suffering from schizophrenia have often been described as less sensitive to emotion and pain. However, it has been shown that despite poor emotional expression and social interactions, patients do perceive emotions. We were interested in finding out whether patients perceive pain better than usually believed as well. We address this question by measuring objective and subjective reactions to acute pain and emotional pictures.

Methods: Twenty-one stabilized and mildly symptomatic patients with schizophrenia and 21 control subjects were included in the present study. We induced acute pain by electrical stimulation and assessed subjective sensations with rating scales, and the neurobiological correlates with early and late Somatosensory Evoked Potentials (SEPs). We also measured cognitive performance, neurochemical components, and subjective and objective responses to visual emotional stimuli.

Results: Our results revealed that, on a subjective level, patients with mild symptoms are at least as sensitive to electrical stimulation and emotional stimuli as controls. This was observed despite the fact that our protocol involved only low-intensity electrical stimulation and moderately negative pictures. The stability of stress hormone levels throughout the protocol confirmed the low intensity of our stimuli. Most importantly, early SEPs were larger in patients than controls after both electrical stimulation and visual processing. This suggests patients' sensitivity is increased.

Conclusions: Taken together, our results disprove the belief that patients are systematically less sensitive to pain and reinforce the idea that, at least on the sensory level, they are hypersensitive to negative stimuli.

Introduction

Patients with schizophrenia are known to be poor at expressing emotions and interacting with other people (1). This led first to the belief that patients do not perceive or feel emotions. More recently, however, this interpretation has been challenged (2; 3). Similarly, since patients suffering from schizophrenia are considered to be poor at expressing pain, in the past it has been thought that they do not perceive it (4–6). Perhaps this point of view ought to be reconsidered as well.

In fact, arguments about what patients can or cannot feel are contradictory. It is generally acknowledged that patients are very sensitive to stressful events, which is a possible vulnerability factor (7), but co-existing with this observation is the idea that they are less sensitive to emotional events (8). These two contradictory observations make it difficult to discern how patients react to different stimuli and situations. Moreover, there could be a difference between chronic stabilized patients, patients in acute phases, and/or unmedicated patients. In particular, it is not clear whether chronic stabilized patients are more or less sensitive to pain and stressful events than controls. This question is very important given that chronic stabilized patients represent the highest percentage of patients suffering from schizophrenia (9).

As emphasized, the literature on pain and schizophrenia rather suggests these patients present a reduction in pain sensitivity. Firstly, historical and recent clinical observations describe patients as being less sensitive to pain or even completely pain-insensitive. The most spectacular observations are concerned with severe self-mutilation, such as complete self-amputation of a hand (10–12). Secondly, numerous case reports describe patients who omit to signal pain in the case of somatic diseases, which often results

in delayed diagnoses and severe repercussions (13; 14). Finally, a number of population-based studies have shown that in population samples of patients with chronic pain, schizophrenia comorbidity is rare (15–17).

Taken together, these observations may prompt the conclusion that patients with schizophrenia are less sensitive to pain than healthy subjects. However, the experimental studies conducted on the subject are not only sparse but also highly contradictory (reviewed in 18–20). Some of them conclude that patients are indeed less sensitive to pain (5; 6), some found no difference at all between patients and control groups (21; 22), and some conclude that patients are even more sensitive to pain than healthy control subjects (23; 24) and have lower pain thresholds for acute pain. Interestingly, Lévesque et al. (24) suggest there may be a dissociation between responses to acute and prolonged pain in schizophrenia, with more sensitivity to acute pain, but less sensitivity to prolonged pain. However, their study was based on a cohort of only 12 patients, and, besides, the majority of experimental studies on pain and schizophrenia rely on subjective responses.

In the present study, our aim was to characterize objective responses to acute pain and negative stimuli, by measuring early and late Somatosensory Evoked Potentials (SEP) after nociceptive stimulation and negative picture presentation. To the best of our knowledge, only one study has ever explored SEP responses to pain in patients with schizophrenia (25). Its authors described reduced subjective sensitivity to electrical stimulation, as well as lower amplitudes of the evoked potentials 100 ms after stimulation. However, the interval between the stimulations was only 1 second, and such short intervals can lead to a sensitization phenomenon resulting in an increase in pain sensitivity in healthy subjects (26). This phenomenon has been shown to be impaired in patients suffering from

schizophrenia, thus inducing a reduction in pain sensitivity compared with matched controls (19; 24). In the present study, we measured responses to acute pain with an interstimulus interval that was long enough to avoid the sensitization phenomenon.

It is furthermore important to characterize the nature of the disturbances in pain perception in patients with schizophrenia, since pain perception involves a range of neurochemical, cognitive and emotion-processing mechanisms (27; 28). From a neurochemical point of view, pain can be expected to increase stress, which can be measured in terms of the amount of activity in the corticotropic axes. It has been proposed for decades that patients with schizophrenia present excessive activity of the hypothalamic-pituitary-adrenal axes (review in 29; 30). We therefore drew up a protocol that allowed us to measure and characterize the reactions of stabilized patients and controls to both acute pain and emotional pictures, by using a multimodal approach involving subjective, electrophysiological, and neurochemical measures. If patients lack sensitivity to pain, we should observe a reduced response to pain, at least on the subjective level. If, by contrast, excessive sensitivity is a key characteristic in chronic stabilized patients, we should be able to objectify a series of heightened responses to pain and emotional pictures.

Material and Methods

Participants

Each group (patients with schizophrenia and controls) consisted of 21 individuals. . Controls were individually matched to patients in terms of gender, level of education, and age (all F's < 1; Table 1). Some EEG recordings included too many artefacts and had to be discarded, but this was not the case in the critical pain condition (see supplementary data for details).

	PATIENTS	CONTROLS
Gender (M/F)	16/5	16/5
Age (mean ± SD)	37.7 ± 9.2	37.4 ± 10.7
Years of education (mean ± SD)	13.3 ± 2.3	13.1 ± 2.3
Medication (typical/atypical/no medication)	5/14/2	–
Dose of chlorpromazine equivalents	244 mg/day	–
Anti-Parkinsonian treatment (tropatepine)	4	
Mean disease duration	12.2 ± 7	
Outpatients/Inpatients	20/1	
PANSS positive symptoms (mean ± SD)	17.5 ± 5.9	–
PANSS negative symptoms (mean ± SD)	21.9 ± 8.2	–
PANSS general symptoms (mean ± SD)	38.2 ± 10.4	–
PANSS total (mean ± SD)	77.6± 10.1	–

Table 1. Demographic and clinical data about the participants.

Pain assessment

We induced pain by means of electrical stimulation. Two electrodes about 3 cm apart were applied to the back of the subject's hand. Each subject underwent two series of 20 successive stimulations, for which each stimulation was announced 3 s in advance and followed by a 30 s interval. During each interval, participants evaluated the stimulation on two successive visual to analogue scales digitized from 0 to 100. They first evaluated the painfulness of the stimulation, from no pain to unbearable pain, and then how unpleasant it was, from very pleasant to very unpleasant.

Each electrical stimulation was a sinusoidal signal with a frequency of 5 Hz and a duration of 50 ms. The two stimulation series differed only in terms of intensity and were separated by about 40 min. The first was a series of low intensity stimulations (1300 μA), the second a series of stimulations of an intensity slightly below the pain threshold (1800 μA).

Tactile sensitivity assessment

Impaired tactile sensitivity might be a confounding factor for pain sensitivity. We used the von Frey filaments to make sure that the peripheral touch receptors were functioning (see details in supplementary data).

Emotion

We tested subjects' reactions to aversive stimuli by using three series of 20 pictures from the International Affective Picture System (IAPS) (31). They differed from one another in terms of their emotional valence and arousal levels (which vary from 0 to 9): *[1]* negative valence (3.6 SD 1.9), high arousal level (6.2 SD 2.1), *[2]* negative valence (3.6 SD 1.7), lower arousal level (4.4 SD 2.2), and *[3]* neutral pictures (valence = 5.0 SD 1.2; arousal = 2.9 SD 1.9).

The pictures were displayed for 5 seconds in the center of a black screen, and subjects had to rate valence from 1 to 9 and arousal levels from 1 to 9 for each picture (see details in supplementary data).

Electrophysiological recordings

An EEG was recorded throughout the emotion and pain assessments using 64+8 multi-channel AgCl active electrodes with a Biosemi® active-two device. The electrodes were mounted on an elastic cap and distributed according to the international 10/20 system (see supplementary data for technical details).

Analysis of pain-related SEPs

We defined EEG epochs from 200 ms before (baseline correction) and 800 ms after pain stimulation in order to measure and compare peak amplitudes of early and late event related potentials. We started by analyzing three components typically related to pain perception: N1 [80-180 ms], P1 [150-210 ms] and N2/P2 [200-500 ms] at the site Cz (32–35).

Examination of the EEG signals suggested there were two additional SEP components in the group of patients with schizophrenia. We subsequently analyzed a very early signal, i.e. the P50 [20-70 ms], as well as a later positive component which started around 210-250 ms after the stimulations.

Visual ERPs

We defined EEG epochs from 200 ms before (baseline correction) to 2000 ms after picture presentation onset so that we could measure both early and late visual ERP's in response to the three different picture types.

The different ERPs we observed were similar to those described in the literature (36–38). We therefore analyzed an early negative component between 100 and 200 ms, a

following complex consisting of a positive peak and a negative peak between 200 and 400 ms, and, thirdly, a late positive potential (LPP) which usually lasts for 6 s. The positivity of the LPP has been correlated to the arousal levels of the emotional stimuli (36). We also observed an additional early positive peak in the patient group between 20 and 70 ms.

Blood sample assessment

We measured plasma ACTH and cortisol levels to assess the activity of the pituitary-adrenal axis before and after the electric stimulations (see supplementary data for details).

Procedure

Each subject participated in two sessions which took place on two consecutive days. On the first day we mainly checked for possible biases (visual acuity, color vision, tactile sensitivity, diabetes, substance use) and tried to reassure the participants by letting them try 6 electrical stimulations, including 1800 µA.

The main part of the experiment took place the following morning. Due to the circadian variations of the hormones measured (ACTH and Cortisol), we made sure all subjects underwent the different tests and provided blood samples at the same time of day (see fig.1 for the actual protocol).

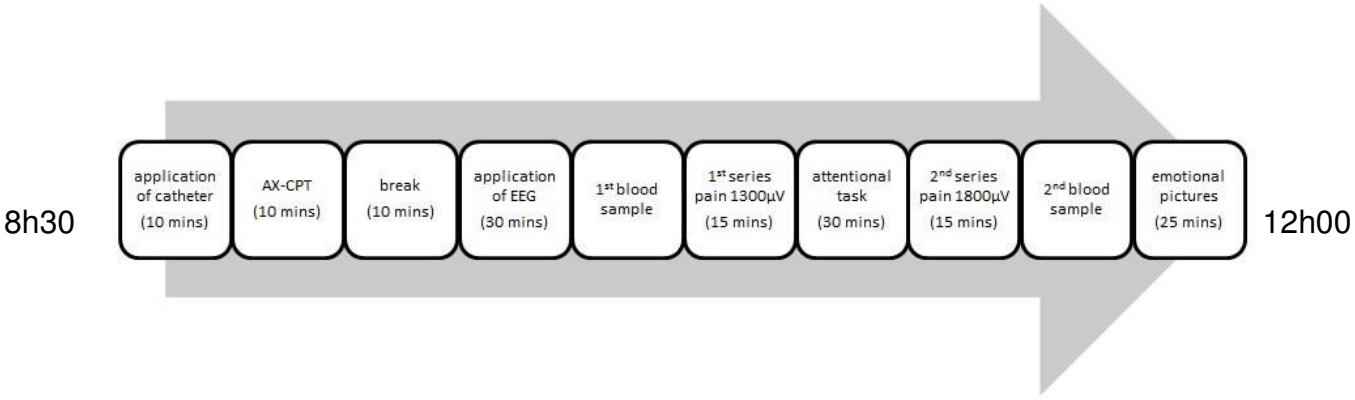

Figure 1. Experimental procedure performed on Day 2. For the sake of simplicity, we have not reported the results of the attentional tasks, because they do not contribute any relevant information. Early application of the catheter avoided any interference with blood sampling by the needle prick.

Statistics

To identify differences between the patient and control group, as well as between the different conditions, we used repeated measures Analyses of Variance (ANOVAs), and dissected the analyses subsequently.

Results

Pain perception

Subjective evaluation

There were two measurements (pain, unpleasantness) for each condition (1300 µA, 1800 µA). The stimulations were rated as significantly more painful and unpleasant in the 1800 µA condition than in the 1300 µA condition in both groups. Patients' pain ratings were slightly, but not significantly, higher than those of controls (Table 2).

	mean (σ)	*mean (σ)*	*F*	*Df*	*p*	*Cohen's d*
Pain						
Intensity	**1300µA**	**1800µA**				
main effect	17.94 (20.4)	24.62 (26.2)	24.13	1,41	<.00005	.29
patients	22.35 (22.1)	31.1 (28.3)	15	1,20	<.005	1.5
controls	13.53 (17.9)	18.13 (22,7)	10.37	1,20	<.005	.95
Group	**patients**	**controls**				
main effect	26.73 (24.8)	15.83 (20.2)	2.43	1,40	.13	-
1300µA	22.35 (22.1)	13.53 (17.9)	2.02	1,40	.16	-
1800µA	31.1 (28.3)	18.13 (22,7)	2.68	1,40	.11	-
Interaction Group × Intensity			.24	1,40	.62	-
Unpleasantness						
Intensity	**1300µA**	**1800µA**				
main effect	50.84 (15.0)	43.98 (17.8)	25.57	1,41	<.00005	.42
patients	50.65 (15.9)	45.45 (18.8)	8.92	1,20	<.05	.4
controls	51.0 (14.5)	42.5 (17.1)	17.11	1,20	<.005	2.6
Group	**patients**	**controls**				
main effect	48.05 (17)	46.76 (15.1)	0.07	1,40	.8	-
1300µA	50.65 (15.9)	51.0 (14.5)	.006	1,40	.94	-
1800µA	45.45 (18.8)	42.5 (17.1)	.28	1,40	.6	-
Interaction Group × Intensity			1.51	1,40	.23	-

Table 2. Subjective rating measurements for both scales in response to painful stimulations (pain: 0 = no pain – 100 = unbearable pain; unpleasantness: 0 = very pleasant – 100 = very unpleasant).

Mechanical pain threshold

There was no significant group effect for tactile sensitivity [F(9, 360)=.37, p=.95]. (see fig S1 in supplementary data).

Pain-related SEP recordings

N1/P1 and N2/P2

At the Cz site, for the 1800 µA intensity, the mean amplitude of N1 in patients was significantly higher than in controls, whereas no difference was found for the 1300 µA intensity. There were no differences between the two groups for the components P1 and N2/P2 (Table 3).

P50/P1*

In patients we observed a very early positive potential, which looks like a P50, at around 20-70 ms at electrode sites Cz and Fz, and a second component of the P1 between 210 and 250 ms, which we shall refer to as a P1*.

For both signals, the ANOVA showed a significant amplitude difference between the two groups in the case of 1800 µA stimulations. The amplitude of the P50 was significantly greater in patients compared to controls at the two sites Cz and Fz. This effect was not significant at 1300 µA (Table 3). We examined the results individually, which allowed us to rule out the possibility that the P50 is an artifact due to the electrical stimulations or is only present in some patients. The P50 started after the stimulation period and was present in the majority of patients (see supplementary data for individual details).

The ANOVA for the P1* revealed a significant between-group difference at the site Fz: the amplitude of the Peak P1* was significantly higher in patients than control subjects for both 1300 and 1800 µA intensities (fig. 2, fig. 3, and Table 3).

Overall, we also observed a slight time lag in the results of patients compared to control subjects. Patients' SEP responses seem to be later than controls' responses, although this difference was not significant for either of the SEP peaks.

	mean (σ) patients	*mean (σ) controls*	*F*	*Df*	*p*	*Cohen's d*
Cz						
P50						
Main effect: Group						
1300µA	6.0 (4.4)	4.0 (5.3)	1.66	1,34	.21	-
1800µA	6.4 (4.3)	2.8 (2.1)	11.78	1,40	<.005	1.1
N1						
Main effect: Group						
1300µA	-6.56 (7.2)	-3.64 (3.3)	2.45	1,34	.13	-
1800µA	-6.25 (6.1)	-3.07 (3.7)	4.19	1,40	<.05	.63
P1						
Main effect: Group						
1300µA	10.45 (6.6)	7.62 (5.3)	1.99	1,34	.17	-
1800µA	10.48 (6.2)	9.0 (4.4)	.81	1,40	.37	-
P1*						
Main effect: Group						
1300µA	5.54 (7.8)	2.1 (6.9)	1.96	1,34	.17	-
1800µA	5.93 (8.5)	1.8 (6.7)	3.08	1,40	.09	-
N2						
Main effect: Group						
1300µA	-8.33 (4.7)	-7.08 (8.8)	.29	1,34	.59	-
1800µA	-8.63 (5.0)	-6.93 (5.4)	1.13	1,40	.29	-
P2						
Main effect: Group						
1300µA	20.63 (5.5)	22.93 (11.7)	.59	1,34	.45	-
1800µA	18.81 (6.9)	18.56 (6.8)	.01	1,40	.91	-
Fz						
P50						
Main effect: Group						
1300µA	7.1 (6.9)	5.2 (5.5)	1.66	1,34	.21	-
1800µA	7.5 (4.8)	4,6 (4.7)	4.03	1,40	.05	.61
P1*						
Main effect: Group						
1300µA	8.29 (8.2)	1.64 (8.2)	5.95	1,34	<.05	.81
1800µA	8.82 (9.4)	1.92 (8.6)	6.14	1,40	<.05	.77

Table 3. Early and late pain-related SEP measurements at the sites Cz and Fz for both intensities.

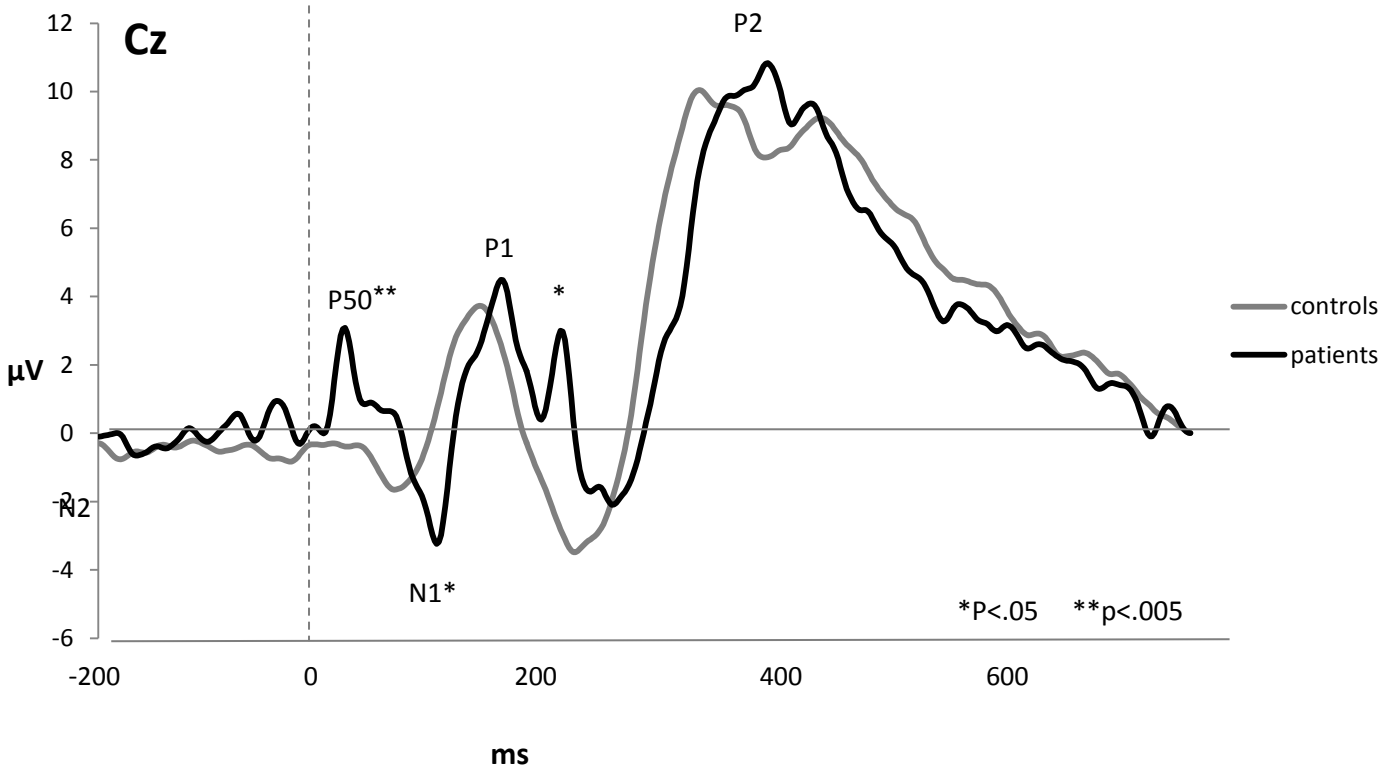

Figure 2. Average mean SEP responses of patients and controls at the site Cz after 1800 µA electrical stimulations. The stimulation started at 0 ms.

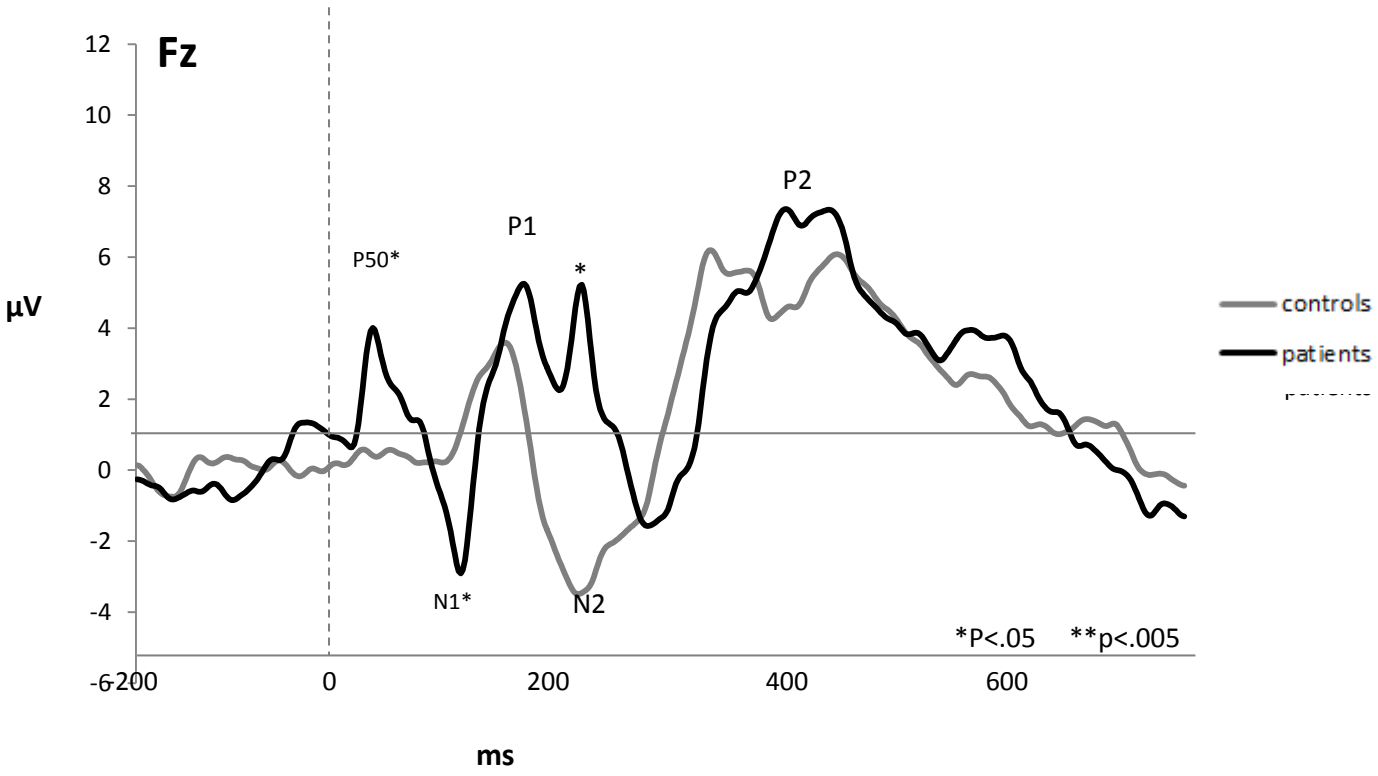

Figure 3. Average mean SEP responses of patients and controls at the site Fz after 1800 µA electrical stimulations. The stimulation started at 0 ms.

Emotion perception

Subjective evaluation

We analyzed both valence and arousal as a function of the within-group factor 'emotion' (neutral, negative low arousal and negative high arousal). No group effect was found for valence. There was a significant effect for arousal. Overall, patients rated the three different kinds of pictures as more arousing than healthy control subjects (Table 4).

	mean (σ) patients	*mean (σ) controls*	*F*	*Df*	*p*	*Cohen's d*
valence						
Main effect: Group	3.9 (0.9)	4.02 (0.9)	.5	1,40	.48	-
Emotion			128.38	2,80	<.0005	-
Interaction Group × Emotion			1.49	2,80	.23	-
arousal						
Main effect: Group	4.45 (2)	3.35 (1.9)	3.98	1,40	.05	.56
Emotion			42.48	2,80	<.0005	-
Interaction Group × Emotion			1.0	2,80	.37	-

Table 4. Mean results of subjective valence and arousal in the two groups. Patients rated the images overall as more arousing than healthy control subjects.

Visual evoked potentials

To analyze the visual evoked potentials in response to the three different types of pictures, we initially averaged Event-Related Potentials (ERPs) for negative pictures with high arousal, negative pictures with low arousal, and neutral pictures separately. The overall shape of ERPs was similar for all three kinds of pictures. There was no interaction between emotion and group but there were several overall effects of group. Accordingly, the results presented have been averaged over all three picture types. The positive ERP P50 and late LPP (1200-1400 ms) were both more pronounced in patients than controls in fronto-central regions (Table 5). On the whole, the peak amplitudes were nonetheless significantly higher for high-arousal pictures, and between-group differences, which are detailed among the supplementary data, were slightly more marked for these pictures.

		mean (σ) patients	mean (σ) controls	F	Df	p	*Cohen's d*
	Fz						
P50							
	Main effect: Group (µV)	4.11 (5.5)	2.7 (2.5)	7.19	1,36	<.05	.53
P2							
	Main effect: Group (µV)	1.69 (6.7)	-0.7 (5.1)	2.53	1,36	.12	-
early	**LPP (400 - 600 ms)**						
	Main effect: Group (µV)	-1.44 (7.9)	-4.81 (6.7)	4.06	1,36	.05	-
late	**LPP (1200 - 1400)**						
	Main effect: Group (µV)	4.44 (7.0)	1.91 (5.5)	5.21	1,36	<.05	.49
	Cz						
P50							
	Main effect: Group (µV)	3.6 (2.7)	2.54 (1.8)	4.56	1,36	<.05	.63
P2							
	Main effect: Group (µV)	3.27 (5.5)	1.56 (4.1)	1.61	1,36	.21	-
early	**LPP (400 - 600 ms)**						
	Main effect: Group (µV)	0.06 (4.3)	-2.06 (5.3)	2.74	1,36	.11	-
late	**LPP (1200 - 1400)**						
	Main effect: Group (µV)	3.91 (4.1)	2.02 (3.7)	4.67	1,36	<.05	.28

Table 5. ERP peak amplitude differences after picture presentation. The results are averaged and combine all three picture types. Main group effects are presented for the sites Fz and Cz.

ACTH and cortisol levels

ACTH and cortisol levels were compared between groups and times (before vs. after electrical stimulations). Patients' levels of ACTH [F(1,40)=3.63, p=.06] tended to be higher than controls', but there was no effect of time. The cortisol level did not differ between times or groups (see supplementary data for details).

Correlations

There were no correlations with equivalent chlorpromazine or clinical symptom.

Discussion

Our results consistently demonstrate that patients suffering from schizophrenia are not, as generally believed, insensitive to pain. If anything, the patients who took part in our study rated electrical stimulations as more painful than controls. This difference was not significant, but the results illustrate that as regards acute pain patients were at least as sensitive as controls. Moreover, the amplitude of SEPs observed immediately after the stimulations was significantly greater in patients than controls. This difference indicates that the nociceptive information is processed and elicits an abnormally large neuronal response. The additional measurements were consistent with these results. Firstly, patients rated pictures as more arousing and, secondly, they displayed greater ERP amplitudes in response to pictures than controls. Overall, our results unambiguously counter the general belief that patients are less sensitive to painful and emotional stimuli.

Our methodology was designed to minimize potential artefactual results. Firstly, we were careful to discard subjects with pain treatments, cannabis abuse, or tactile sensitivity disorders, which was confirmed with urine screening and the von Frey filaments. Secondly, heightened sensitivity to pictures and electrical stimulations cannot be explained away by a non-specific attention deficit or general deficit because both should have produced the opposite pattern of results. Indeed, our electrical stimulations were rather weak, and a non-specific sensory impairment should have led to decreased rather than increased responses. An interaction between antipsychotic drugs and our data also seems unlikely, given that antipsychotic drugs induce emotional flattening (39). Antipsychotics should thus have lessened rather than increased responses to pain or pictures.

Overall, our results clearly demonstrate that patients are generally more sensitive to painful and emotional stimuli than controls, a finding consistent with the idea that patients are more sensitive to stressful or negative stimuli (40; 41). Our results further suggest that this hypersensitivity can be observed even in the case of low-intensity pain stimulations and only moderately negative pictures. Thus the hypersensitivity occurs independently of stress effects. Anyway, as shown by the stability of the cortisol and ACTH results, our equipment and stimulations were not stressful enough to elicit a release of stress hormones. An excess of released stress hormones is observed mainly in the case of metabolic stress, in acute phases of psychosis, or in non-treated patients (30; 42–45). The lack of significant group effect for cortisol or ACTH in our study is thus not surprising.

Our results on emotion perception are also consistent with the recent literature, which suggests that patients are more sensitive than believed previously to the emotion conveyed by visual information (46), and with studies showing hyper reactivity to neutral pictures (47). Our results on pain may seem more surprising but are consistent with recent results obtained by Lévesque et al. (24), according to which patients present a reduced sensitivity to chronic pain but an increased sensitivity to acute pain. In our study, we chose to separate the electrical stimulations by a 30 s interval and, consequently, tested the effects of acute rather than chronic pain.

All in all, our results are not as surprising as they may seem at first sight. Moreover, they provide original evidence to supplement the literature. Our approach is original in that we examined reactions to stimulations by means of objective measurements (*i.e.* early potentials evoked by electrical stimulations). The early responses (50 ms after stimulation) are those most clearly amplified in patients when compared to controls. By 100 ms, the

increase in the amplitude of the evoked potentials is still apparent, but less clear-cut, and the subjective response is not significantly different from that of controls. The P50 amplitude increase after the pain stimulations and emotional pictures shows that the alteration affects the earliest levels of processing, not only the subjective report. Interestingly, abnormally high amplitudes of P50 have been observed in the context of sensory gating due to a lack of suppression of early signals (48). Although the paradigm in the present study is clearly different, our results are consistent with the idea that patients with schizophrenia have difficulty filtering incoming information on the basis of past experiences (49). It is a hypothesis further supported by the presence of a second SEP peak at 250 ms in patients after pain induction. This peak and its occurrence in time resemble the P300a which has been previously correlated to the novelty of a stimulus (50). The presence of the additional peak in patients but not controls could mean that patients process each stimulation as a new and unpredictable event, whereas for controls this information would be anticipated and would not represent a novelty. Each stimulation was in fact announced verbally, meaning it was possible, at least for healthy controls, to anticipate the pain. Finding a deficit in anticipation in patients would be consistent with a number of empirical results (51–55). However, an increase in the amplitude of this SEP is certainly surprising in patients with schizophrenia, insofar as the P300a amplitude is usually described as being decreased, especially during the oddball test. In fact, this decrease is one of the best replicated results in patients (56). However, the explanation for this discrepancy may be the major differences between the oddball and our tasks. During the oddball test, the P300a is elicited by an effect of surprise due to an unexpected event occurring within a series of regular and predictable events. With our task, however, the target stimulation is predictable, and in fact no P300a was expected, and none was observed in controls. The peak observed at 250 ms in patients

is thus an abnormal reaction to a predictable event, rather than a normal orientation of attention towards a deviant. Consistent with aberrant saliency (57), it would reflect an abnormal attention orientation towards repetitive stimulations.

It should be noted that with our protocol this interpretation is all the more plausible given that we prepared the subjects at various stages of the protocol in order to avoid any nocebo effects (58; 59). On the first day, we reassured participants by stressing that the stimulations were not very intense and by actually showing them what they were like. Modulation of pain perception by top-down control appears to involve complex mechanisms (60; 61), and our suggestion that stimulations were of low intensity, coupled with the announcements made before each stimulation, may have helped control subjects to gate nociceptive information. Such control mechanisms may not have worked as well in patients with schizophrenia (62).

Regardless of the mechanisms underlying these impairments, our study showed that stabilized patients with schizophrenia react more intensely than healthy controls to acute electrical stimulations and negative pictures. Our data unambiguously show that patients are not indifferent to their environment and reinforce the idea that they are abnormally sensitive to negative emotion. Interestingly, this was the case with stimuli that were not very intense. The electrical stimulations for acute pain were of low amplitude, and the pictures presented were only mildly negative. Even though these results were obtained in chronic/stabilized patients, and they cannot be generalized to patients in acute phases who self-mutilate, they suggest that low-intensity stimulations (1800 µA electrical stimulations, negative pictures) affect patients more than controls. This could mean patients experience more difficulties than controls when processing sensory information with a negative

emotional valence. Our results show that it is important to measure responses to emotional as well as painful stimuli by means that do not require a verbal or behavioral statement.

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2.1. Supplementary material 1

Material and Methods

Participants

The project was approved by the local ethics committee, and informed written consent was obtained from each subject, in accordance with the recommendations of the Declaration of Helsinki. All subjects had normal or corrected-to-normal visual acuity. Psychiatric diagnoses and the Positive and Negative Syndrome Scale (PANSS) (1) scores were established by senior psychiatrists from the Psychiatry Departments of the Universities of Strasbourg and Besançon on the basis of semi-structured interviews and the MINI. Patients, whose state had to be stable for them to be included in the study, fulfilled the criteria for the diagnosis of schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Exclusion criteria for patients and controls were: the intake of benzodiazepines and painkillers, a history of alcohol and drug dependency, neurological and medical pathologies (especially diabetes), a disabling sensory disorder, and general anaesthesia in the 3 months prior to testing. A urine sample was analyzed in each case to eliminate the existence of cannabis abuse. An additional exclusion criterion for controls was psychotropic medication in the 3 weeks prior to testing.

In the pain condition with minimal intensity, EEG recordings included too many artefacts in 6 subjects (3 patients/3controls), who were thus excluded from the analysis of 1300 µA stimulations. For the same reason, 4 subjects (2 patient/2 controls) were excluded from the EEG analysis of emotional pictures.

Von frey filaments

This test consists of nylon filaments with varying diameters which are pressed against the skin until the filament is curved. We chose 10 different diameters which were each tested 20 times on the back of the subject's hand, in random order. The intensity of the stimulation increases with the diameter of the filaments, such that it is possible to quantify subjects' touch sensitivity. They were asked to close their eyes and to signal verbally when they felt they had been touched.

Emotion pictures

The experiment was run on a Pentium 4 PC. The stimuli were displayed on an Iiyama monitor (21-inch, 85 Hz refresh rate). E-prime 2 was used to program and automatize the whole procedure, and the order of the pictures was semi-randomized. Each picture remained on the screen for 5 seconds. After each picture, subjects rated valence and arousal levels on the visual analogue scales SAM also presented on the computer screen. The SAM consists of a row of graphic figures that range from smiling and happy to frowning and unhappy, with 9 levels ranging from 1 to 9 to represent the hedonic valence dimension. For the arousal dimension, SAM figures range from relaxed and sleepy to excited and wide-eyed, again with 9 levels from 1 to 9 (2). As soon as the rating was complete the next picture was displayed.

EEG

The EEG signal was sampled at the rate of 2048 Hz (0.01–100 Hz bandpass filter, 12 dB/octave), and the reference electrodes were located at both earlobes (averaged off-line). Eye movement artefacts were monitored with additional electrodes, measuring vertical and horizontal electrooculographic bipolar potentials, and EEG recordings were corrected off-line

with an Independent Component Analysis procedure (3; 4). Brainvision Analyzer software (Brainproducts, Munich, Germany) was used to process the results off-line.

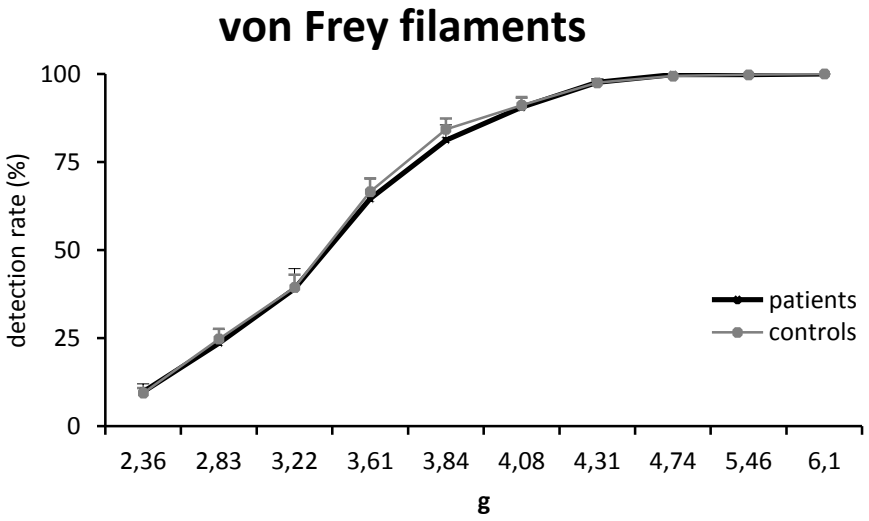
Blood sample

Blood was sampled in lithium heparin tubes (LH-PSTII tubes; Becton Dickinson, Le Pont de Claix, France) before and after the electric stimulations. When subjects arrived for the experiment a catheter was inserted in the crook of one of their arms to prevent any interference from the pain induced by the needle prick during blood sampling. The first blood sample was taken 50 min after the catheter had been inserted and before the first series of pain stimulations. The second blood sample was taken 5 min after the second series of stimulations.

ACTH and Cortisol concentrations were determined by means of electrochemiluminescence immunoassay on Cobas E 601 (Roche Diagnostics, Indianapolis, Indiana, USA) according to the manufacturer's instructions. The intra and inter-day accuracy of the methods used was between 5 % and 10% for the routine quality control.

2.2. Supplementary material 2

Results



S1. Detection rate of tactile sensation as a function of the pressure of the von Frey filaments (patients vs controls).

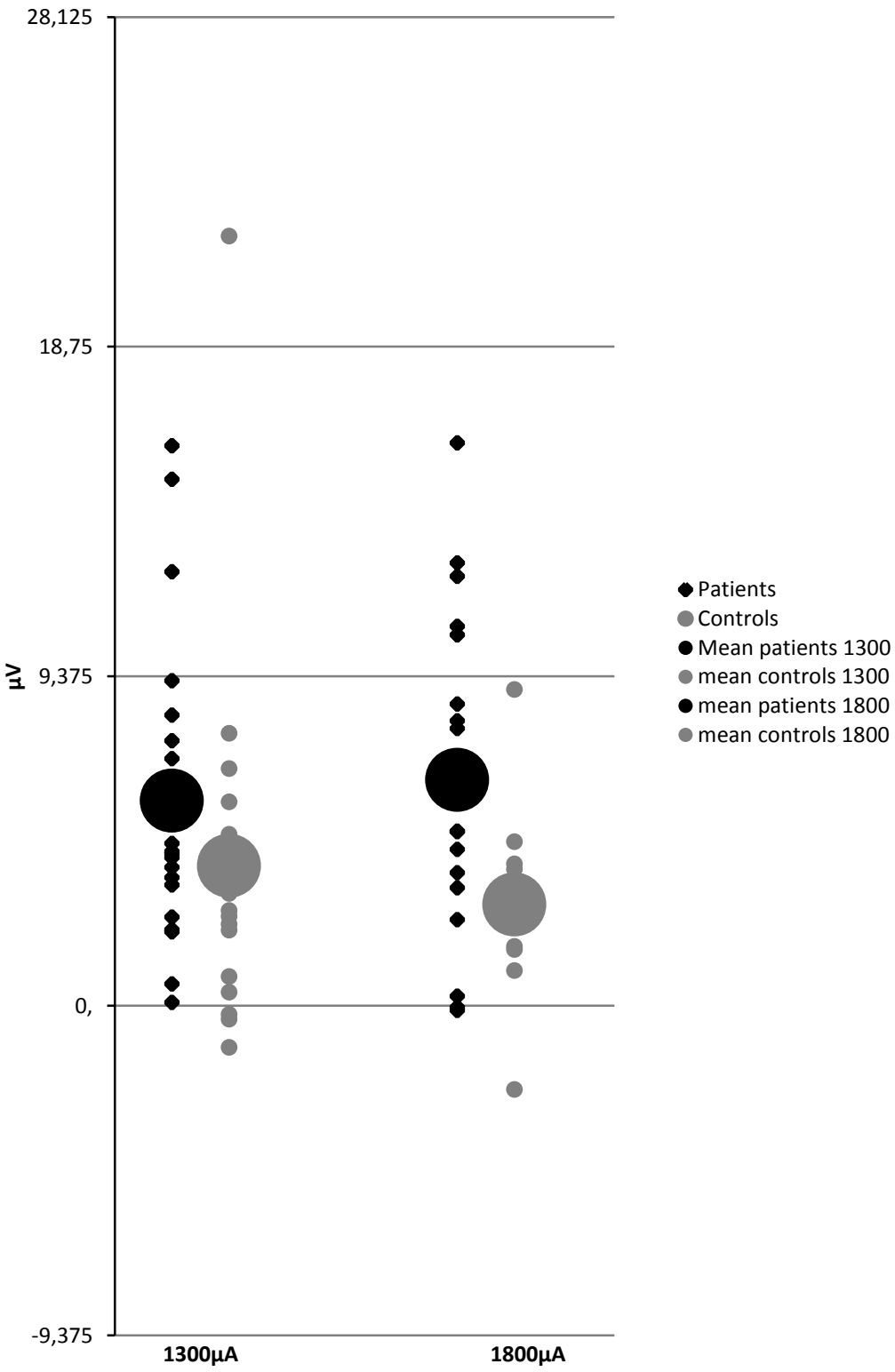
	mean (σ) patients	mean (σ) controls	p (patients/controls)
Cortisol (nmol/L)			
Before stimulation	424.7 (189.8)	361.9 (140.2)	0.17
After stimulation	413.0 (151.3)	368.2 (103.7)	0.33
p (before/after)	0.80	0.89	
ACTH (pmol/L)			
Before stimulation	6.33 (3.8)	4.77 (1.9)	0.22
After stimulation	6.85 (6.69)	4.76 (2.0)	0.10
p (before/after)	0.68	0.99	

S2. Comparison of blood sample results between patients and controls based on an ANOVA and a subsequent Fisher's LSD post hoc analysis.

negative high arousal	*mean (σ) patients*	*mean (σ) controls*	*F*	*Df*	*p*	*Cohen's d*
Fz						
P50						
Main effect: Group (µV)	4.63 (3.3)	2.25 (3.5)	4.62	1,36	<.05	.88
P2						
Main effect: Group (µV)	3.64 (5.9)	-1.32 (5.5)	7.2	1,36	<.05	.8
early LPP (400 - 600 ms)						
Main effect: Group (µV)	1.45 (7.2)	-3.48 (8.3)	3.82	1,36	.06	-
late LPP (1200 - 1400)						
Main effect: Group (µV)	7.65 (5.2)	2.84 (7.3)	5.45	1,36	<.05	.82
Cz						
P50						
Main effect: Group (µV)	4.01 (2.2)	2.25 (2.0)	6.53	1,36	<.05	1.0
P2						
Main effect: Group (µV)	5.35 (5.4)	1.85 (4.8)	4.46	1,36	<.05	.88
early LPP (400 - 600 ms)						
Main effect: Group (µV)	3.11 (4.9)	0.96 (6.6)	1.31	1,36	.26	-
late LPP (1200 - 1400)						
Main effect: Group (µV)	5.99 (4.0)	4.11 (4.1)	2.03	1,36	.16	-

S3. ERP amplitude differences between patients and controls in respect of highly arousing pictures at sites Fz, Cz and Pz.

S4. ERP responses of patients and controls in respect of negative high arousing pictures at the site Fz. Picture onset was at 0 ms.



S5. Individual P50 amplitude data in both pain conditions. Mean data for each group is shown as a big circle.

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Chapter 3: Discussion

In order to discuss the results on pain perception and to go a little bit more into detail, we will individually consider the different components of pain perception, and discuss their relation to possible alterations in schizophrenia. Therefore we will add some supplementary data which we did not describe in the paper for the sake of simplicity.

Our results are surprising, considering the contrast they present to clinical observations. They might thus raise some questions which we will try to discuss here.

3.1. Physiology and anatomy

First of all, we have to consider the influence or interaction of some of the different neurotransmitters that have been shown to play a role in schizophrenia as well as pain. It has been shown that acute phases in schizophrenia are accompanied by a hyper activation of the dopaminergic system and that medications which block the activation of the dopaminergic receptor D2 reduce schizophrenia symptoms (de Manzano, Cervenka, Karabanov, Farde, & Ullén, 2010). The brain regions that are affected by this dopaminergic activity concern especially the thalamus as well as the striatum (de Manzano et al., 2010).

As we have previously seen, one of the most important cerebral structures implicated in pain perception is the thalamus, and it has been shown that dopamine plays a role in multiple levels of pain processing in the thalamus. In Parkinson, a decrease of dopaminergic activity has been correlated to an increase of pain perception (Jääskeläinen et al., 2001). Thus it is tempting to assume that in schizophrenia this result could be inversed leading to a decrease in pain perception due to an increase in dopaminergic activity. This was not the case. On the contrary we observed an increase in responses to pain. However our patients were medicated and medication is supposed to regulate dopamine. There was no correlation

with medication and besides, we measured HVA levels, which represent an index of dopamine activity. The absence of differences between HVA levels in patients and control subjects (as shown in table 8) suggests there was no difference in the activity of the dopaminergic pathways. This conclusion should be taken with caution, since HVA was measured in the blood, and can only poorly reflect the central effect of dopamine. However, we have no evidence that dopamine abnormalities explain our results.

	mean (σ) patients	mean (σ) controls	F	Df	p
Dopamine (ng/mL)					
Main effect: Group	70.29 (39.2)	145.94 (357.5)	.93	1,40	.34
Time			1.46	1,40	.23
Interaction Group × Time			.23	1,40	.63
Adrenaline (ng/mL)					
Main effect: Group	55.37 (35.17)	65.12 (60.9)	.41	1,40	.53
Time			.02	1,40	.89
Interaction Group × Time			2.94	1,40	.09
Noradrenaline (ng/mL)					
Main effect: Group	150.75 (102.5)	109.94 (69.2)	2.24	1,40	.13
Time			.08	1,40	.77
Interaction Group × Time			.02	1,40	.89
VMA (ng/mL)					
Main effect: Group	0.4 (0.3)	0.34 (0.2)	.88	1,40	.35
Time			1.2	1,40	.27
Interaction Group × Time			2.5	1,40	.12
HVA (ng/mL)					
Main effect: Group	1.55 (0.8)	1.06 (0.9)	3.62	1,40	.06
Time			.34	1,40	.57
Interaction Group × Time			1.05	1,40	.31

Table 8. Comparison of blood sample results between patients and controls.

Even if our results cannot be explained by dopamine alterations, they still stand in contrast to the reports psychiatrists make about their patients.

The most important results were those that we obtained with the EEG, thus a recording of voltage changes in response to our painful stimuli. This technique has its limits;

the most important one is a bad spatial resolution. This has to be taken into account while analyzing the results; however the strength of this technique is a very good temporal resolution. We showed that there is a significant difference between patients and controls in a very early stage of pain processing. Patients showed an abnormal response right after the painful stimulations which was almost completely absent in healthy controls.

Considering the complexity of the different interacting top down and bottom up processes that are implicated in pain processing, our results can be explained by a possible top down inhibitory mechanism. The existence of these endogenous inhibitory mechanisms can be measured with diffuse noxious inhibitory control paradigms. DINC is triggered by nociceptive stimuli which recruit inhibitory neurons located in the brainstem that project to the spinal cord and dampen the intensity of incoming afferents (Le Bars, Dickenson, & Besson, 1979). Potvin et al. (2008) have shown that this mechanism is intact in patients when the inhibitory pathway is triggered by a noxious stimulus. Interestingly, a recent study by Goffaux et al. (2007) has discovered that anticipation can modulate this mechanism. In their study both the nocebo and placebo mechanisms were tested. They showed that subjects who did expect to feel more pain after the DNIC, felt more pain, and those who did expect to feel less pain after the DNIC, did actually feel less pain. These results were corroborated by ERP recordings. This paradigm might be a good way to test whether patient's anticipation for painful stimuli is actually impaired. Such a study may be all the more interesting since anticipation in general might be altered in patients suffering from schizophrenia. We briefly develop this aspect in the following section.

3.2. Cognitive processes

Anticipation as well as attention, are two cognitive processes which might be implicated in the alteration of pain processing observed in patients. As we have already stressed, it is possible to reduce or heighten pain perception simply by altering subject's expectations. However, in order to anticipate an event that has been announced or that can be predicted, one has to be able to look forward in time. Interestingly, it has been recently shown that temporal order judgments (Capa, Duval, Blaison, & Giersch, 2014) and elementary mechanisms of time predictions might be impaired in patients (Lalanne, van Assche, & Giersch, 2012; Lalanne, Van Assche, Wang, & Giersch, 2012). These results suggest that it is difficult for patients to follow and anticipate events over very short intervals in time. One possible explanation for our results is thus an inability of connecting the announcement of the stimuli with the actual stimulation.

Another maybe complementary explanation is a deficit in attention. During this study we measured attentional mechanisms with the CPTax. The test consisted of a series of 4 letters (A, B, X, Y) which appeared successively in the middle of the screen for 6 minutes. Each letter was displayed for 250 ms and the interval between the successive letters was 750 ms. Subjects had to react and press the space bar only when A was followed by an X and not in any of the other possible sequences (A Y, B X). The proportion of sequential pairs of letters was manipulated, with 80% AX sequences (160 times), 10% BX (20 times), and 10% AY (20 times). Attention was measured by evaluating reaction times and error rates in the AX condition; in this condition, errors represent misses. Error rates for the condition AY (false alarms) measure the ability to inhibit an anticipated response, and BX error rates (also false alarms) represent contextual errors.

The results were decomposed into two kinds of measurements: response times and error percentages. In addition we checked the evolution of performance with time, and compared performance during the first half of the experiment vs. the second half. Interestingly, for the response times there is a significant interaction between group and time (first half vs. second half of the task) [$F(1,40)=4.67$, $p<.05$; $\eta_p^2=.1$]. Patients' performance deteriorated over time, whereas healthy controls improved their performance (fig.17). Such a deterioration was also observed for the misses (AX errors). In the second half of the experiment patients made significantly more errors than healthy controls [$F(1, 40)=5,56$, $p<.05$] (fig.18). These results suggest that patient's attention may decline over time. Although this should have led them to be less sensitive to stimulation, it may also have led them to prepare themselves less for the announced stimulation. This may have led to a decrease of gating mechanisms.

Taken together, either of these cognitive processes or both can be at the origin of the heightened sensitivity to painful stimulations in patients. However the reactions to negative and neutral pictures are difficult to explain solely in terms of decreased anticipation and highlight that the underlying impairments are even more complex.

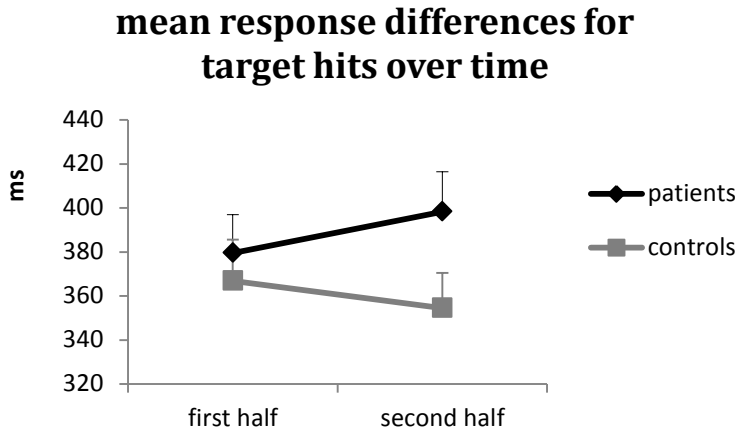

Figure 18. CPTax: mean response times with SEM for the target hits (AX) over time. Patients performance deteriorates over time whereas healthy controls become faster.

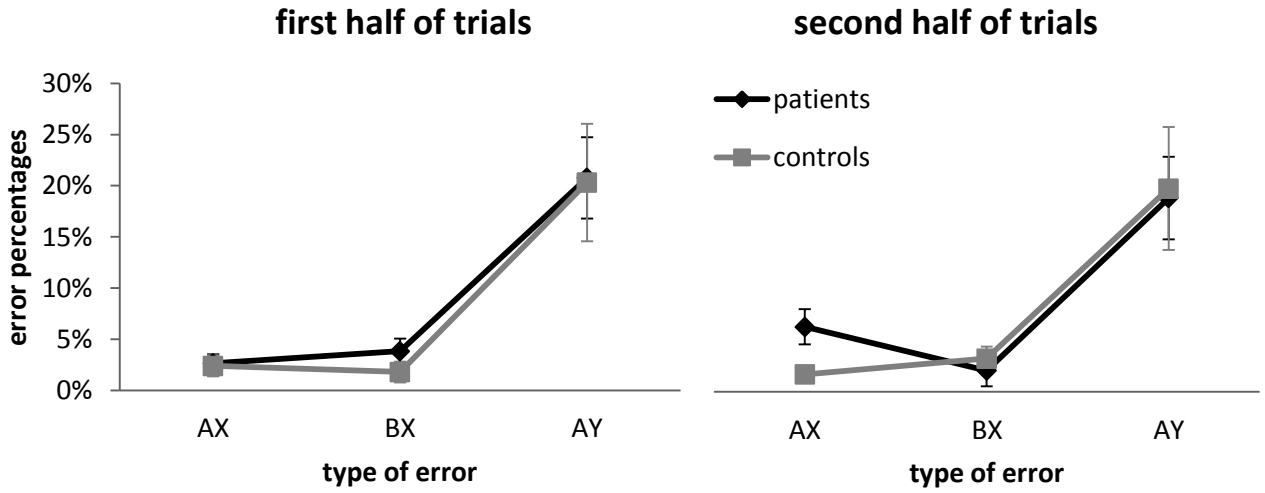

Figure 19. CPTax: mean error rates with SEM over time in patients and controls, for each type of errors (AX errors represent misses, whereas BX and AY errors represent false alarms. In the second half of trials patients make more misses.

3.3. Affective and behavioral processes

The two things to be noted here are the behavioral results, thus the subjective evaluation of the painful stimulation, as well as both subjective and physiological responses to visual emotional stimuli. As a reminder, the subjective evaluations were differentiated in two components for the painful as well as the visual stimuli. The electrical stimulations were evaluated as more or less painful from 'no pain' to 'unbearable pain' and second as more or less unpleasant from 'pleasant' to 'very unpleasant'. Patients rated the painfulness of the stimulations as slightly higher in both conditions, however this difference was not significant, and there were no differences at all in the evaluation of unpleasantness (fig.19). Thus there is a dissociation between an heightened early physiological response and the lack of any group effect in the behavioral data at least for the unpleasantness rating. There are at least two possibilities to explain this dissociation. On the one hand patients could have developed a compensating strategy in order to bear heightened sensitivity. The second abnormal ERP peak that occurred around 250-350 ms might be evidence that there is a supplementary process effective in patients. This might be the result of a pain blocking mechanism that could otherwise overwhelm them.

On the other hand, this dissociation could be linked to an altered subjective evaluation of emotional stimuli. The evaluation of neutral stimuli might also be considered as aberrant inasmuch patients seem to allocate more importance to neutral stimuli and evaluate them as more arousing than healthy controls do (Lakis & Mendrek, 2013).

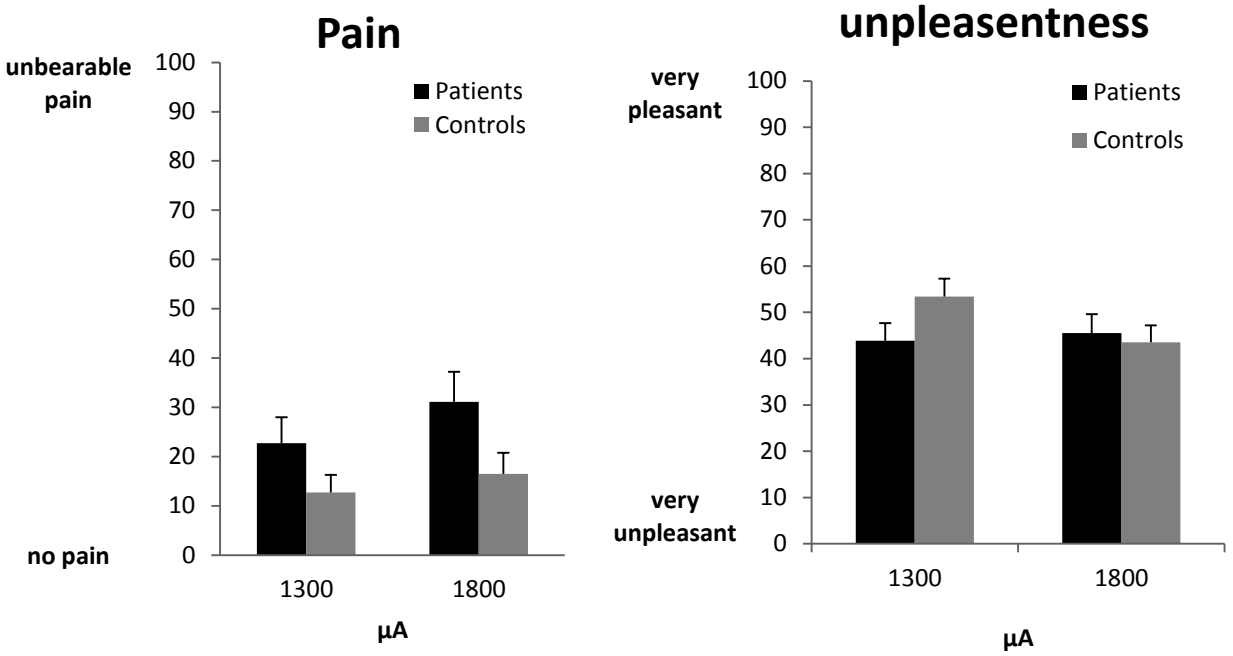

Figure 20. Mean subjective pain and unpleasantness ratings for patients and healthy controls. Each subject underwent two series of 20 stimulations, the first with an intensity of 1300 µA the second with an intensity of 1800 µA. There were no between group differences not for category and not for intensity either.

3.4. Impaired inhibition or a nocebo effect?

We have already evoked the possibility that this heightened pain sensitivity in patients is due to a lack of anticipation and thus impaired inhibition of the nociceptive signal. We have proposed cognitive explanations for the lack of anticipation. This lack of anticipation might also be facilitated by the clinical symptoms of the patients, e.g. anxiety. It is possible that healthy controls believed us, and remembered the stimulations as not very intense, whereas patients were not able to take our explanation or their own previous experience into account. This might lead them to inhibit the pain less, or even to have a reverse effect of the

stimulation announcement. Such an effect might have participated to the results on pain. It probably does not explain the whole pattern of results, though. First it would not explain the results on neutral pictures. Second it should have induced an effect at the subjective level, which was not observed. Finally, patients did not appear to fear the electrical stimulations. In fact, most of the patients, who refused to participate, did so because of the blood sample and not the electrical stimulations.

3.5. Dissociation: what psychiatrists observe vs. our results

Our results stand in contrast to what psychiatrists observe in their practical experience. There are different possible explanations for this discordance.

First of all, it has to be considered that the patients who participated in this study were all clinically stabilized and were only mildly symptomatic. These characteristics might be different for those patients who have committed severe self-mutilations. Indeed the review by Large, Babidge, Andrews, Storey, & Nielssen (2009) describes that such behaviors are mostly observed in first episode psychosis. In addition, Song & Yi (2000) (in Potvin & Marchand, 2008) have shown that pain insensitivity increases with the severity of positive symptoms. Thus the patients' state could explain the differences between our study and clinical observations.

Another possibility that might explain this discordance could be the circumstances that differentiate our experimental condition from a painful situation in real life. We have to keep in mind that during our experiment, the subjects were in a very artificial situation and we asked them explicitly to rate their pain after the stimulation. This is hardly ever the case in real life where patients as well as everybody else, have to initiate a pain evaluation on

their own. Thus in respect to our results, we cannot exclude that this initiation is impaired in everyday life and that the insensitivity to pain observed clinically in patients is due to a lack of pain response initiation and thus pain expression.

Besides, our results should not be generalized to all pain conditions. As already emphasized in the manuscript, Levèsque et al. (2012) have suggested that chronic patients are less sensitive to chronic pain but not to acute pain. Despite these limitations, our results underline the fact that patients are not insensitive to pain. These results may incite psychiatrists and anesthetists to reconsider their assumptions about pain perception in patients and to adjust the treatment individually to each patient. We have already talked about the fear of blood samples that seems to be intense in patients and which could be linked to this hypersensitivity to stimuli of moderate intensity.

3.6. Men vs. Women

A great debate has always been the question of sex differences in pain perception. Women are usually convinced that they can bear more pain than men, however men do not agree and vice versa. As a matter of fact in a lot of research studies have shown that women are more sensitive to pain than men (Fillingim & Maixner, 1995) which may be due to many factors as for example social pressure (real men don't feel pain) (Robinson et al., 2001).

Therefore we thought it would be important to analyze sex differences in our results on pain, even though our groups did only include 6 women. We thus analyzed interaction between sex and group for the SEP P50 and the subjective evaluations of painfulness and unpleasantness for the intensity 1800 µA.

There was no significant interaction between group and sex for either one of the measurements, however the graphs leave room to suspect that there are some differences at least in patients. It seems as if the elevated sensitivity is more pronounced in men than in women (fig.21). Future studies should take this possibility into account.

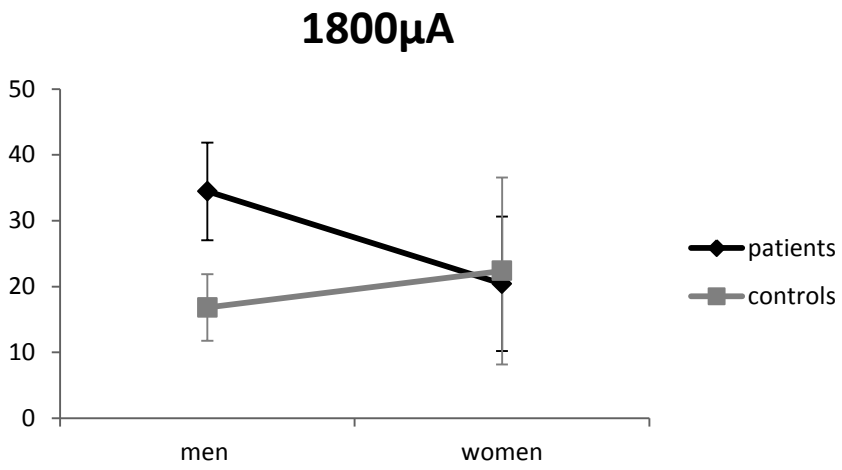

Figure 21. Differences between men and women for subjective ratings for the stimulations with the intensity 1800 µA .There is no interaction between sex and group [F(1, 38)=1.09 ; p=.3].

Part 4

General Discussion

and

Conclusion

Chapter 1:
General Discussion

1.1. Patients are more sensitive than previously thought

The two studies we presented are very distinct which is why we have treated them individually throughout the manuscript. However they share a common global frame and goal. Primarily, research on schizophrenia is aimed at better defining this mental illness and understanding the mechanisms of the clinical impairments in order to improve treatment, medical care as well as the patients' quality of life. Both studies share a very general characteristic, inasmuch they both contribute to better understand some aspects of the cognitive impairments observed in patients, and more specifically which components of emotion, perception and pain are impaired or preserved. This brings us to the second common characteristic of the two studies which both address perceptual deficits and their interaction with emotion. Emotion in schizophrenia has always been a debated question in respect to perception as well as expression. The blunted affect, a symptom frequently encountered in schizophrenia, describes patients as poorly expressive. This has led to the assumption that they don't perceive emotion. This assumption has been attenuated, but deficits in emotion perception and expression are still attested clinically and empirically (Kring & Moran, 2008).

Besides, recent theories and studies have attested a strong interaction between emotion and cognition, with specific mechanisms for different cognitive functions (Pessoa, 2008). In memory, emotion can improve consolidation, in visual perception emotion can attract attention, and in pain perception it is necessary to evaluate the aversive character of the pain (Bushnell et al., 2013; Carretié, Mercado, Tapia, & Hinojosa, 2001; Ohman et al., 2001; Sutherland & Mather, 2012; Villemure & Bushnell, 2002). Considering the deficits in pain perception, visual perception and emotion perception encountered in patients, as well

as the role emotion plays in cognition in all subjects, our global interest was to elucidate how emotion and perception interact in healthy volunteers (part 1) and the outcome of this interaction in patients (part 1 and 2).

With the results we gathered here, it is possible to speculate about the nature of the emotion perception deficit in schizophrenia. We have already discussed the results for each study individually in the respective sections, thus we will briefly extract the important results that present similarities and pave the way for more general hypotheses. Both studies parted from the general belief of diminished responses to salient stimuli in patients with schizophrenia. The literature on the behalf of pain as well as emotion perception is however discordant. Here we demonstrate repeatedly and by means of different measures and studies that patients are not as insensitive as they are often described and imagined. More precisely, we show by means of EEG measures, that patients present a heightened sensitivity to painful stimulations as well as negative visual stimuli at a very early stage of processing. Furthermore we observed differences between patients and healthy controls, in the subjective ratings of these stimuli by means of VAS. Patients rated neutral as well as negative stimuli (different categories from the IAPS as well as faces) as more arousing than healthy controls. There were no differences in valence ratings of the visual stimuli or in subjective pain and unpleasantness ratings. As a reminder the differences observed in arousal ratings correspond to the extent of calmness and excitation. Subjective arousal ratings have been correlated to autonomic responses which are the automatic physiological responses that can be triggered by emotional stimuli (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000). Valence ratings on the other hand correspond to a cognitive interpretation of the pictures (negative/positive).

Taken together, the EEG results suggest a heightened sensitivity at an early processing level that might correspond to heightened arousal. These results are consistent with a study by Williams et al. (2004), which has shown that patients have heightened skin conductance responses in response to neutral as well as fearful faces. Williams' and our results might seem to present a huge discrepancy to the literature, but this is not necessarily the case. In fact, perceptual mechanisms, such as emotion and pain perception, require complex cognitive and physiological processes which can be sub divided into different components (i.e. pain can be roughly sub divided into sensation, cognitive evaluation, emotional evaluation and expression). Therefore it is possible that our results represent the heightened sensitivity occurring at an early processing stage whereas studies that have shown reduced sensitivity might represent an impairment occurring at later processing stages. This might mean that physiological sensitivity is preserved or even heightened, but that this sensitivity is not expressed. We have developed three possible explanations that further support our hypothesis. We will go a little bit into detail on these theories however we would like to stress beforehand that these theories are merely speculative. Nevertheless, in respect to the existing literature, these speculations are plausible and give directions for further research.

First of all, the literature on emotion perception is vast and we have to keep in mind that there are several distinctions that have to be made. The flat affect described in patients may be the end result of different processes, and discussing our results in the light of the literature requires taking into account the different processes potentially involved in the patients' deficits. Depending on the methodologies, experiments measure the experience of emotion or the outward expression of emotion. The first one is most often evaluated on the basis of the subjective and verbal report of the patients, whereas the second one can be

measured by recording the facial expression variations in patients. Furthermore facial emotion perception may itself be disturbed, which includes a third perceptual mechanism that should not be confounded with the other two. In the case of facial emotion recognition, subjects have to judge the emotion of a peer. This recognition does not necessarily require the experience of the emotion expressed on the face (Kring & Moran, 2008). It is thus important to keep these differences in mind when interpreting the results. In our case, we have different measures which allow us to differentiate between the experience of emotion and the expression. We may interpret the EEG responses and arousal ratings as reflecting the experience of patients, whereas the evaluation of the picture valence and of the pain intensity would be closer to the expression. According to this interpretation, patients would have heightened early responses to emotional and painful stimuli, but this heightened sensitivity would not be expressed. For pain evaluation this means that our stimulations are not evaluated as more painful, and for the emotional stimuli, the higher sensitivity does not translate into valence judgments.

Thus it is possible that these effects are linked to a lack of expression in patients. Indeed, a dissociation between sensation and expression has often been described in patients (Kring & Moran, 2008). Two additional elements may also subtend some discrepancies between clinical observations and our results, i.e. a lack of self-initiation of subjective judgments, or a deficit in conscious access. Patients do not rate the stimulations as less painful than healthy controls, and do not evaluate pictures as less negative or positive. This stands in contrast to clinical observations that suggest a poor facial expression in response to emotional stimuli (Kring & Moran, 2008), and a lack of verbal report in case of somatic pain (Murakami et al., 2010; Retamero & Paglia, 2012). This contrast between our results and clinical observations may be due to the fact that we ask for a judgment, whereas

in everyday life such judgments are spontaneous. Indeed, in everyday conditions the emotional evaluation of our environment, as well as the expression of pain and the seek for help, has to be self-initiated. Judgments may be altered in clinical settings because they are not self-initiated. Self-initiation has already been proposed as being disordered in patients with schizophrenia (Danion, Huron, Vidailhet, & Berna, 2007). In our task, the fact that patients are explicitly instructed to make a judgment may compensate for their initiation difficulty.

Yet the initiation of subjective judgments includes another process that lies in-between sensation and expression, i.e. the conscious access, which could explain impairments just as well. Conscious access is necessary to emit subjective judgments. If affected, it might result in lack of spontaneous evaluations, but might be partially compensated for if an explicit judgment is required through instruction. Impaired conscious access has already been proposed in schizophrenia by Del Cul et al. (2006). It is to be noted that it is probably not specific to schizophrenia, as it is also impaired in multiple sclerosis (Reuter et al., 2007, 2009). It remains nonetheless to be seen if this impairment in conscious access is more marked when emotional information is involved. Besides it might be asked whether information is dampened at a lower level than the access to consciousness. Our experiment on pain has shown that reactions to emotional pictures are increased at a very early stage of visual processing in patients. Given these pictures have an arousing effect, they should attract attention automatically. However, in our paradigm on perceptual organization, there is no evidence of a distracting effect of neutral or negative pictures in patients. This lack of effect is unlikely due to a difficulty in conscious access, since emotional pictures had only an incidental influence. Besides, the preserved effect of positive faces in patients suggest that faces were processed by patients like controls. It remains to be

understood why the heightened arousal effect of negative and neutral background faces had no behavioral consequences.

There is still an alternative explanation for our results, though. The results on pain may suggest that patients dampen their perception to avoid being overwhelmed by emotional or pain information. There was indeed no amplification in late signals and in subjective reports despite a large and early amplification of the visual evoked potentials. A similar effect was observed on pictures. Inasmuch the evaluation of the valence corresponds to a cognitive interpretation of the pictures, these results would once again suggest a dissociation between the automatic and early processing of emotional information, which would be rather amplified, and the cognitive interpretation of this same information, which would be dampened. Instead of being the result of an impairment at the cognitive level, the effects would thus be the result of a compensation mechanism for a hypersensitivity at the lowest levels of processing. This kind of pain inhibition is different from the one resulting from gating mechanisms. In our paradigm we supposed that controls were able to prepare for the pain and to inhibit the transmission of the signal in advance. In patients the heightened early evoked response in EEG certainly suggests that there is no early inhibition. If the signal is dampened in patients with schizophrenia, this inhibition mechanism would occur at a later, subjective stage. This may especially occur if patients do not anticpate the pain or emotion signal, but react to it.

Overall, when taking both our results and the literature, there seems to be a differentiation between early processing stages and the behavioral expression of patients with schizophrenia. We think that the continuation of this study is worthwhile and might give further insight into the mechanisms of this discrepancy. We will thus briefly discuss

some of the limits that have to be considered in further research and continue with some possible perspectives for future studies.

1.2. Limits of this study

Several aspects have to be kept in mind, and should be changed or further elaborated in order to confirm the hypotheses that we have elaborated.

First of all, the patients we tested were stable and medicated. In patients with schizophrenia these two variables are important to consider but not easy to control. We did not include patients who took benzodiazepines in this study, and we tended to exclude an effect of antipsychotics. We included only stable patients, which was on the one hand necessary since the protocol required subjects that could bear the EEG and could sit still over a long period of time, and secondly because they represent a large percentage in patients with schizophrenia. However, we certainly cannot generalize our results to the whole population of patients, especially as our sample sizes remained modest. This also probably explains that we did not find correlations with clinical symptoms. Studies on larger samples may be required to explore the link between our observations and blunted affect.

A second limit is related to our choice of stimuli. In both studies we chose inoffensive stimuli as to not put the patients in a situation that might offend or stress them unnecessarily. We limited the intensity of the electrical stimulations and we selected pictures that were only mildly positive or negative. Of course this makes it difficult to affirm that we actually measure pain, or that we induced emotion. The stimuli may have been too inoffensive for healthy subjects, and we cannot know what would have happened with more negative pictures or electrical stimulations of higher intensity. However these characteristics

also underline the importance of our results, as we show not only that patients are not insensitive to pain or emotion, but also that they have a heightened sensitivity even for very mild stimuli.

1.3. Perspectives

With our research we have provided some answers in respect to emotion and cognitive processing in patients with schizophrenia. However with these answers and the hypotheses we have deduced, we also gathered more questions. We can classify the perspectives into four different categories.

1. For the first study on the effect of emotion during visual organization, one important question remains that we haven't been able to answer yet. The positive faces we used were not very expressive which stands in contrast to the literature on the behalf of emotional faces (Becker et al., 2011). The common stimuli that are used in order to test the perception of emotion expression are usually taken from batteries that include portraits of actors who express one emotion explicitly. We used the portraits of faces in the IAPS which seem more authentic. These differences and the fact that these kinds of faces are not commonly used to explore face processing in schizophrenia make it difficult to understand why these faces have such a strong effect on attention. One possible explanation could be that the attraction is linked to social mechanisms. A likable face might incite to look for social contact or interaction. In further studies it would be interesting to address this question more deeply in order to determine why these faces capture so much attention. Therefore we could start with a paradigm during which we ask participants to attribute different adjectives to these pictures. Furthermore we could try other kinds of faces, or eliminate further confounding factors. Positive and negative faces that we used were taken from

different individuals. This could be controlled for, if we take one positive and one negative picture for each model. However this will only be possible if we know what characteristics the positive picture needs in order to create such a strong attraction.

2. The second interesting question category concerns the preserved effect of positive faces in patients with schizophrenia. As already mentioned, the perception of facial expression has been shown to be impaired in patients with schizophrenia. However the faces used in these studies are very expressive. It is thus possible that we did not measure the same effect at all. Nevertheless it is interesting to consider the literature which suggests that the ocular exploration scan path is reduced for faces in patients (Loughland, Williams, & Gordon, 2002; Minassian, Granholm, Verney, & Perry, 2005; Toh, Rossell, & Castle, 2011). This effect is all the more marked when the task does not require subjects to explore faces and exploration is spontaneous. The alteration of the scan path disappears when the task incites subjects to look at the face features (Delerue, Laprévote, Verfaillie, & Boucart, 2010). This stands in contrast to our results. In our task indeed, the effect of the faces was incidental, and it is thus all the more surprising that their distracting effect was preserved. It would be useful to replicate these results with eye tracking measurements, which would give more insight into the actual similarity between the results in patients and healthy controls. It would help to understand how patients explored the stimuli and whether the preservation of the distracting effect is specific to the positive faces we used. Indeed, we have excluded a role of low-level physical characteristics in our stimuli, by using faces displayed upside-down. It may still be possible however, that the saliency of the faces is detected on the basis of preserved information processing (Laprévote, Oliva, Delerue, Thomas, & Boucart, 2010). Laprévote et al. (2010) have used hybrid faces, which are composed of two superimposed faces, one with only low spatial frequency content, and one with a high spatial frequency

content. Depending on the distance between the pictures, subjects will see either the picture with a low or with the high spatial frequency content. Patients were biased towards the pictures with low spatial frequency content, suggesting that this processing is preserved. It might thus subtend the effect of positive faces in patients. It could be possible that what makes an upright face attractive and interesting is subtended by low spatial frequencies.

Furthermore, the use of other emotion categories in patients would give some clarity. This could help to define whether the preserved sensitivity to the positive faces is a special case or whether emotion perception in our paradigm can be generalized over categories.

3. The third category of questions concerns the specificity of pain in patients. We have already discussed some possible subsequent studies for the experiment on pain perception in schizophrenia. Here we will briefly resume that different aspects should be considered more closely. First of all, it would be interesting to conduct a follow up study in order to confirm that the absence of a P50 in controls, actually corresponds to an endogenous inhibitory control mechanism. This could be measured by replicating the same experimental conditions, with one exception: we could solely change the way we describe the stimulations to the participants. Since we hypothesized a possible placebo effect in healthy controls, we might get a different result if we describe the stimulations as painful or if we do not describe them at all.

It could also be interesting to replicate this study with fMRI recordings that might indicate whether top down pathways are activated. Regions of interest could be the anterior cingulate cortex as well as the parietal operculum/posterior insula, as they have been shown to present increased activity to nonpainful stimuli, when subjects expected pain (Sawamoto et al., 2000). Furthermore, as already mentioned in the previous section, we could try to

replicate in patients the paradigm by Goffaux et al (2007) which has shown the effect of expectation (placebo and nocebo) on the perception of painful stimuli in healthy subjects.

4. The last sort of possible perspectives has emerged in relation with the global meaning of our results. We hypothesized that our results stand for a discrepancy between early processing of emotional stimuli and the subjective response. The next step would be to determine whether patients do not express their emotions/pain or whether they have difficulties evaluating the actual meaning of these stimuli. To that aim we might record the facial expression of patients concomitantly with EEG and verbal reports when emotions are elicited by negative videos or narratives.

Chapter 2:
General Conclusion

As discussed in the introduction, patients with schizophrenia suffer from multiple symptoms and cognitive impairments. In addition they are avoided and/or feared in society as the definition of schizophrenia is still vague and rather complicated. Patients' representations in the media are often false and induce a general belief of them as being dangerous. Furthermore, as the definition is not complete, many scientists as well as people from medical staff may add assumptions to their own representations of schizophrenic patients, which influence and guide their way to treat the patients. It is thus important to consider these assumptions and findings in an empirical way, especially when they affect important cognitive mechanisms, as for example emotion and pain perception.

In this manuscript we have presented two studies that address two of these assumptions in distinct ways. Patients are thought to be less sensitive to pain and emotion. Both our studies disprove these beliefs and suggest that a generalization of these beliefs is not possible. With these two experiments we show that patients are not as insensitive as they were thought to be. In some respects, here for painful and neutral stimuli, they even seem to be more sensitive than healthy controls. For neutral stimuli and pain, this has already been shown; however for both kinds of stimuli we added a more objective measure which can underline these findings. For painful stimuli we used ERP measures of the brain activity which objectified this hypersensitivity and added a notion of time. In respect to healthy controls, increased responses occurred at a very early processing stage which allowed us, together with other measures, to hypothesize that this hypersensitivity could be linked to a lack of anticipation.

The impact of emotion was measured in the two experiments subjectively and objectively, however with different means. In the experiments on visual perception we used a cognitive visual grouping task. Contrary to the results obtained in the study on pain

perception, here the objective measures did not confirm the hypersensitivity for neutral stimuli. Indeed the behavioral results (response times) were not different between the two groups, and the neutral images did not have a supplementary impact on the performances in the visual grouping task. However with the latter we were able to show that at an early processing level, positive faces have the same distracting effect on patients as they have on healthy control subjects. These discrepancies between objective measurements and subjective evaluation seem to indicate that emotional processing can be normal in patients, however their conscious evaluation seems to be distorted.

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Annex

Negative stimuli interfere with visual organization

Introduction

In this part we will develop the results in the “semantic category” animals and we start by detailing those from Experiment 1 in the article. As a reminder, in Experiment 1 background pictures belonged to one of four possible semantic categories. Like for faces, the category animals led to a significant interaction between the factors “emotion” and “connectedness” [$F(2, 28)=5.13$, $p<.05$; $\eta_p^2=.27$].

Thus we pursued the analysis on this category with a post-hoc HSD Tukey test, which showed a significant grouping effect when the two targets are associated to a positive [connected = 864ms; unconnected = 1055ms; difference = 191ms; $p<.05$] or an incongruent [connected = 894ms; unconnected = 1044ms; difference = 150ms; $p<05$] background. In contrast there was a complete disappearance of this grouping effect when targets were associated to a negative background [connected = 915ms; unconnected = 945ms; difference = 30ms; $p=.46$] (fig.1).

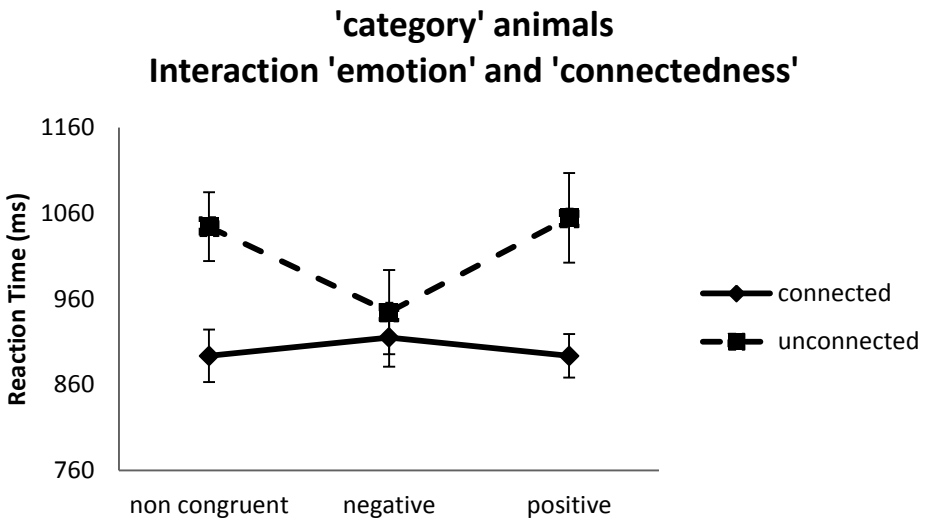

Figure 1. Graph depicting the results of the first Paradigm in the "semantic category" animals
Mean RTs with SEM, averaged over subjects, as a function of the type of emotion conveyed by the background pictures (on the x-axis). The dashed line stands for unconnected targets and the continuous line for connected targets. The effect of grouping vanishes when the targets are associated to two pictures of animals with a negative valence.

These results were confirmed by an ANOVA sub-analysis conducted on each "emotion" condition: there was a significant advantage for connected targets when the background behind the targets was composed of two pictures of animals with non congruent valences (positive and negative) [$F(1, 14)=11.09$, $p<.05$; $\eta_p^2=.44$] or two animals with a positive valence [$F(1, 14)=8.37$, $p<.05$, $\eta_p^2=.37$]. In the condition with two animals with a negative valence in the background the difference between connected and unconnected targets was abolished [$F(1, 14)=.57$, $p=.46$; $\eta_p^2=.04$]. To conclude, in this category we observe a grouping effect which vanishes when the two background pictures are animals with a negative valence.

Experiment Animals

In this experience we sought to replicate the results of the first study in the "semantic category" animals only, and to check whether these animal pictures were not a grouping factor on their own. Therefore we constructed two successive paradigms.

Material and Method

We used the same images of animals as in Experiment 1 and created two new paradigms. The first one was identical to Experiment 1 but with a more important number of trials. Again we had six conditions with two intra group factors: "connectedness" (connected vs. unconnected), and "emotion" (positive congruent, negative congruent, non congruent), leading to a total of 144 trials with 24 trials per condition (fig.2A).

For the second paradigm we deleted the bars which created the grouping factor "connectedness" like in Experiment 3. There was thus only one condition: "emotion" (positive, negative and non congruent) (fig.2B). Each subject ran the two paradigms consecutively, first the one with connecters and secondly the one without connecters.

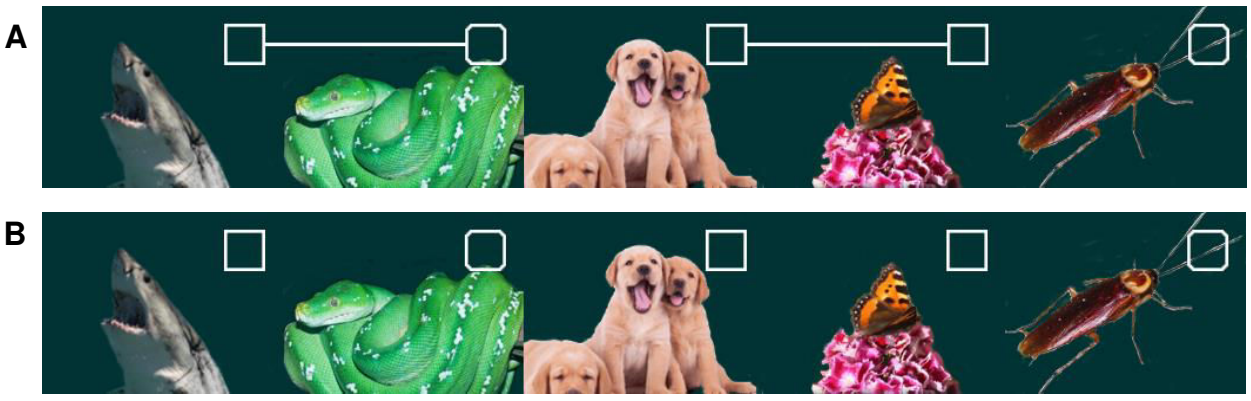

Figure 2. Examples for the stimuli used in Experience 5
A depicts an example of the stimuli with the factors "connectedness" and "emotion" **B** illustrates the stimuli with the factor "emotion" but without the factor " connectedness". The pictures exposed here are not the original pictures. We created these examples in order to respect the publication conditions for the use of the IAPS picture database (Lang et al., 2008).

Results and discussion

This experiment was conducted with 33 students of the university of Dijon (26 women, 7 men, mean age = 19 years). Due to the change of location, we had to slightly change the material. There was no response box, thus the response buttons were the keys “f” and “j” on the keyboard.

With the first paradigm we were able to replicate the previous results i.e. the overall ANOVA analysis revealed a significant interaction between the factors “emotion” and “connectedness” [$F(2, 64)=4.04$, $p<.05$; $\eta_p^2=.11$]. Furthermore the post-hoc Tukey test as well as the individual sub-analysis for each emotion condition, showed again that the advantage for connected over unconnected targets was abolished when the two targets were located on two pictures of animals with a negative valence [HSD Tukey post-hoc test: (connected = 976ms; unconnected = 995 ms; difference = 19ms; p=.68); sub-analysis: $F(1, 32)=.17$, $p=.68$; $\eta_p^2=.01$]. In the incongruent condition, the advantage of visual grouping by connectedness is significant (connected = 890ms vs. unconnected = 1004ms; difference = 114ms; $p<.05$), and in the positive condition, this difference tends towards significance (connected = 908ms vs. unconnected = 997ms; difference = 89ms; p=.053) (fig.3).

The second paradigm revealed no difference between the different emotion conditions (non congruent, negative and positive) [$F(2, 64)=2.23$; $p=.12$; $\eta_p^2=.07$]. This demonstrates that the emotion conveyed by the pictures is not a grouping factor on its own. The effect found in the other paradigms appears to result from a similar effect of distraction as in the previous experiences with emotional faces as distractors. Even though the results are less clear cut, and we do not observe an inversion of grouping effect, they show that like for positive faces, the emotional valence of the negative animal pictures distract the subjects to an extend that this alters their performances.

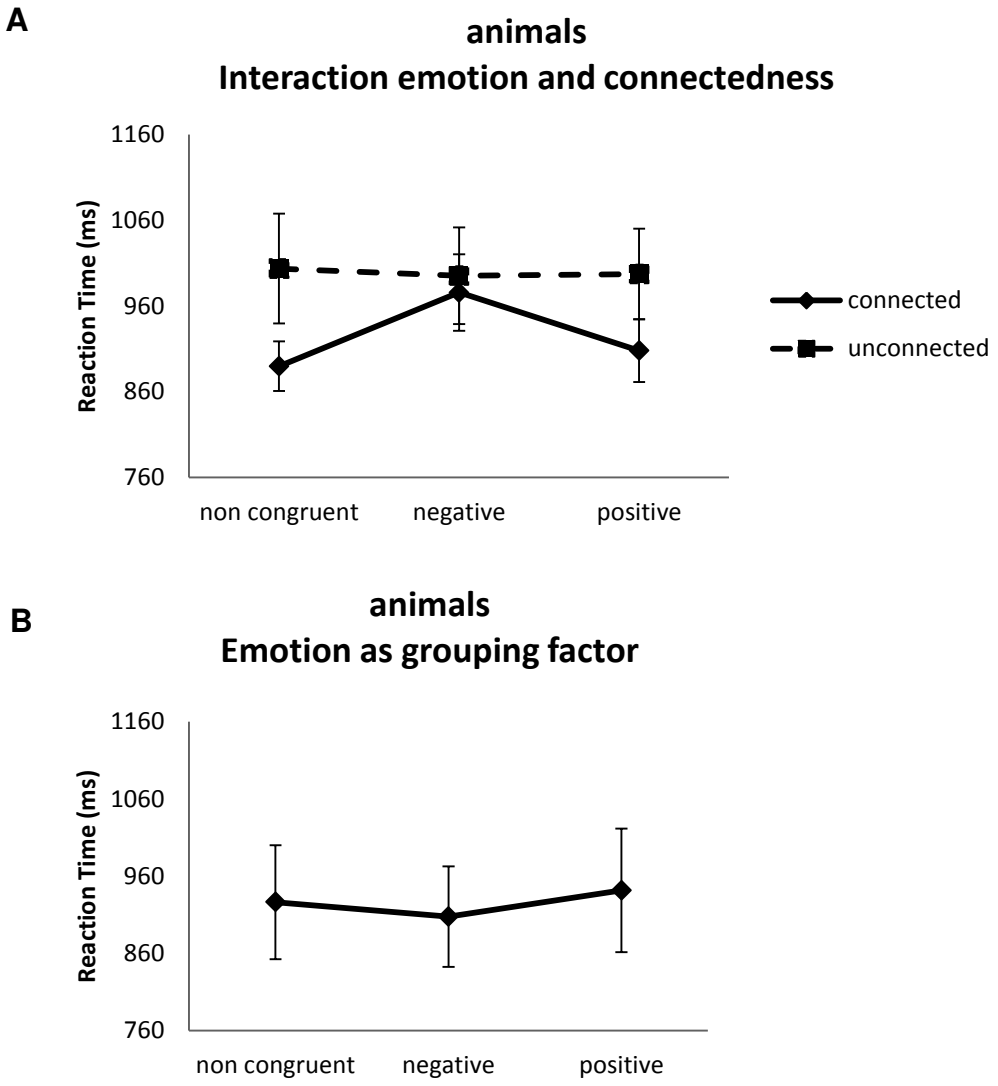

Figure 3. Illustration of the results depicting the interaction between "emotion" and "connectedness", with connecters (***A***) and without connecters (***B***).

A RTs with SEM are averaged over subjects and represented as a function of the emotional valence of the two pictures that lie behind the targets (on the x-axis), and of the two grouping conditions (dashed line = unconnected targets; continuous line = connected targets). Non congruent signifies that the targets are placed on one negative and one positive picture. The grouping effect is abolished when the targets are located on two pictures of animals with a negative valence.

B In the control condition (without the factor connectedness), there was no effect of "emotion". These results indicate that the abolition of the grouping effect is due to the emotion conveyed by the pictures rather than an artefactual consequence of the background pictures.

To be noted, the comparison of the two graphs might suggest a slight difference between the results of the two Experiments with animals: although not significant, RTs seem to vary for connected targets in the first Experiment, whereas they seem to vary for unconnected targets in the last one. A difference between experiments could not be confirmed statistically. The ANOVA analysis was conducted as described above, with an additional inter-group factor, the Experiment (first vs. second). The interaction between "emotion" and "connectedness" was confirmed [$F(2, 92)=8.14$; $p<.05$; $\eta_p^2=.15$] whereas there was no interaction between "emotion", "connectedness" and the experiment [$F(2, 92)=.53$, $p=.59$; $\eta_p^2=.01$].

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Pain perception in schizophrenia, and relationships between emotion and visual organization: is emotion flattened in patients, and how does it affect cognition?

Schizophrenia is a severe mental illness affecting 1% of the population, and comprises positive (hallucinations) and negative symptoms (blunted affect), but also cognitive deficits. Here we describe two distinct studies which address the question of how emotion and cognition interact, in healthy subjects and in schizophrenia. In the first study we created a paradigm that shows how emotional stimuli distract subjects and thus interfere during the organization of visual stimuli. The effect is the same in patients and healthy controls.

In our second study we explored pain perception by taking into account different mechanisms, and especially emotion processing. The results show that patients are more sensitive to pain than healthy controls as they present an elevated P50 which indicates an alteration at an early stage of processing.

Both studies reveal that patients are more sensitive as previously thought which has to be considered when dealing with patients in hospitals and everyday life.

Keywords: Schizophrenia, Pain perception, emotion, visual perception, EEG

La perception de la douleur dans la schizophrénie et la relation entre l'émotion et l'organisation visuelle de l'environnement: est-ce que les émotions sont perturbées chez les patients, et comment cela affecte-t-il la cognition?

La schizophrénie touche 1% de la population et comprend des symptômes positifs (hallucinations) et négatifs (affect émoussé), mais aussi des troubles cognitifs. Ici nous présentons deux expériences qui explorent l'interaction entre cognition, douleur et émotion chez les patients et les sujets sains. La première étude montre que des images émotionnelles peuvent détourner l'attention jusqu'à renverser les effets de groupement automatique. Cet effet est présent chez les patients comme chez les témoins.

La deuxième étude est centrée sur la perception de la douleur en prenant en compte les différents mécanismes sollicités, dont le traitement émotionnel. Nos résultats, et notamment une P50 élevée chez les patients après la stimulation douloureuse montrent une hypersensibilité à un niveau très précoce.

Les deux études montrent que les patients sont plus sensibles aux stimuli émotionnels et douloureux que ce que l'on pensait, ce qui devrait être pris en compte lors de leur prise en charge.

Mots clés : Schizophrénie, douleur, émotion, perception visuelle, EEG