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Impact of reward on pain threshold and tolerance to experimental pain (Cold Pressor Task) in healthy subjects and patients with schizophrenia

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ABSTRACT

Reduced pain sensitivity is considered as a potential endophenotype of schizophrenia.
Patient's motivation in pain experimental studies was neither assessed nor controlled.
This study aimed to assess the effect of reward on pain in patients with schizophrenia compared to controls.
Rewarded subjects showed higher pain threshold and tolerance compared to unrewarded subjects. Pain tolerance was significantly lower in patients than in controls when they were not rewarded. Reward resulted in an increase of pain tolerance with a higher manner in patients.
This study suggests that better control of motivational aspects could improve assessment of pain sensitivity in schizophrenia.

1. Introduction

It has been known for over half a century that patients with schizophrenia tend to have lower sensitivity to pain (Hall and Stride, 1954; Davis et al., 1979; Stubbs et al., 2015). Many case reports on patients with schizophrenia who seemed not to feel pain despite suffering from serious medical illnesses (e.g. acute abdomen pain, ruptured appendix, peritonitis, peptic ulcers, perforated bowels, fractures, myocardial infarctions, etc.) contributed to this hypothesis of pain insensitivity (Wojakiewicz et al., 2013). Although this hypothesis remains controversial (Engels et al., 2014), a recent review showed that patients with schizophrenia have an overall deficit in clinical pain perception (Antioch et al., 2015).

Furthermore, recent meta-analysis by Stubbs et al. (2015) on experimental pain in schizophrenia showed that pain threshold (defined as the point at which a stimulus, usually one associated with pressure or temperature, activates pain receptors and produces a sensation of pain) and tolerance (defined as the level of pain someone is able to endure) were higher in patients than in healthy subjects.

These results are of crucial importance, since schizophrenia is frequently associated with other morbidities. Thus, insensitivity to pain could represent an additional barrier to accessing medical care (Antioch et al., 2015).

Pain sensitivity deficits in schizophrenia are difficult to explain and likely to be multifactorial. Several neurobiological processes could explain these deficits (Stubbs et al., 2015), especially involving functional alterations in primary sensory regions associated with pain (S1, sensory discriminative pathway), the prefrontal and medial temporal cortices (motivational affective component), the mediodorsal thalamus and the hippocampus (affective and cognitive component).

Cognitive impairment and negative symptoms may also influence the patient's expression of pain (Urban-Kowalczyk et al., 2015). Concerning the motivational aspect, pain is suppressed or enhanced by factors such as predicted reward (Navratilova and Porreca, 2014). Nevertheless, in the experimental pain studies in patients with schizophrenia, the motivation of the participants was neither assessed nor controlled, even though this factor could influence pain perception.

This study aimed to assess the effect of a reward on the pain threshold and pain tolerance of patients with schizophrenia compared to healthy subjects, with the hypothesis that financial reward would increase pain threshold and tolerance in both groups.

2. Methods

2.1. Subjects

50 outpatients suffering from schizophrenia (according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition) and 50 age-matched controls were included. All subjects gave written informed consent to participate, and the study was approved by

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the local ethics committee (Ambroise Paré Hospital, France).

Patients had been under stable antipsychotic medication for at least two months, and their psychopathology had been assessed using the positive and negative syndrome scale (PANSS, Kay et al., 1987). The 50 control subjects with no psychiatric illness, nor family history of schizophrenia, were recruited from hospital staff and the general community through Internet advertising. All subjects with a clinical history of peripheral neuropathies, upper limb trauma, chronic pain conditions, drug intoxication and alcohol dependency, or subjects under antalgic treatment, were excluded.

2.2. The "Cold Pressor Task" procedure

The Cold Pressor Task was first documented as a test of cardiovascular stress reactivity (Hines and Brown, 1936). This tool is now used as a validated tool to assess experimental pain (Von Baeyer et al., 2005). It evaluates pain threshold and tolerance by immersing a subject's hand into cold water, which is maintained at 4 °C using an appropriate device (DIP Cooler, TECHNE, UK). "Pain threshold" was defined as the time (in seconds) when the subject starts to feel pain, and "pain tolerance" was when a subject could no longer keep his/her hand in the water. For ethical considerations, the experiment was ended when tolerance was longer than 180 s.

2.3. Award description and assignation

The study took place in two independent strata. The first strata consisted of fifty subjects (25 patients and 25 controls) who underwent the experiment without attribution of the reward. The second strata consisted of fifty subjects (25 patients and 25 controls), who were compensated by a reward of 70 euros, which was paid via bank transfer following completion of the experiment.

2.4. Statistical analyses

Statistical analyses were performed using SPSS21 Software (Chicago, IL). A two-way analysis of variance was performed to examine the influence of pathology (patients with schizophrenia/healthy subjects) and reward (presence/absence) on pain threshold and pain tolerance. When the assumptions of equality of variances (Levene's test) or the normal distribution of the data (Kolmogorov-Smirnov's test) failed, a log transformation was applied to the data. Partial eta squared (η^2) was used to estimate the size of the effect. Post hoc analyses were performed with Tukey's test.

3. Results

The demographic and clinical characteristics of the four sample groups are presented in Table 1. All participants (n = 100) were included in analyses. Their pain threshold and pain tolerance are illustrated in Fig. 1.

Regarding pain threshold, the Pathology by Reward interaction effect (F[1,94] = 0.465; p = 0.497) and the main effect of Pathology (F [1,94] = 0.558; p = 0.457) were not significant. Yet, the main effect of reward was significant (F[1,94] = 50.566; $p < 0.001$; $\eta^2 = 0.350$ *(large effect size)*), with a higher pain threshold in rewarded groups (mean (SD) = 26.69 (26.70) seconds) than in unrewarded groups (mean(SD) = 8.94 (6.90) seconds).

As for pain tolerance, analysis revealed a significant Pathology by Reward interaction effect (F[1,96] = 7.877; p = 0.006; $\eta^2 = 0.076$ *(moderate effect size)*): the impact of reward (increase of pain tolerance) was higher in patients with schizophrenia compared to controls. In addition, there was a significant main effect of reward (F[1,96] = 42.087; $p < 0.001$; $\eta^2 = 0.305$ *(large effect size)*), with higher pain tolerance in rewarded groups [mean (SD) = 70.54 (57.74) seconds] than in unrewarded groups [mean (SD) = 27.33 (35.55) seconds]. No significant main effect of pathology was found (F[1,96] = 2.104; p = 0.15).

When tolerance was longer than 180 s in patients or in controls, experiment was ended: 8% of the schizophrenic patients (4 rewarded patients and 0 unrewarded patients) and 14% of the controls (5 rewarded controls and 2 unrewarded controls) reached this maximum tolerance. According to analyses conducted with the Chi-Squared test, reward had a significant effect on the proportion of subjects with a pain tolerance greater than 180 s ($\chi^2 = 5.005$, p = 0.025), but not pathology ($\chi^2 = 0.919$, p = 0.338).

Table 1
Demographic and clinical characteristics of subjects.

	Patients with schizophrenia		Healthy controls	
	Rewarded (n = 25)	Unrewarded (n = 25)	Rewarded (n = 25)	Unrewarded (n = 25)
Age	37.84 (9.62)	37.00 (11.60)	35.92 (13.06)	33.52 (8.70)
Sex Ratio	9 W/16 M	10 W/15 M	17 W/8 M	17 W/8 M
PANSS	62.29 (23.28)	65.53 (22.13)		

Legends. Mean (Standard Deviation) are reported; PANSS: Positive and Negative Syndrome Scale; W: women; M: men.

4. Discussion

To our knowledge, this study is the first to investigate the effect of reward on pain threshold and tolerance in patients with schizophrenia and healthy controls. Regarding either pain threshold or pain tolerance, there was no significant effect on pathology. The proportion of patients whose hand immersion exceeded 180 s was not different from the control group proportion. However, in the unrewarded groups, pain tolerance was significantly lower in patients. This result is in accordance with Girard et al. (2011) who reported a lower experimental pain threshold (mechanical pressor or ischemic pain) in patients with schizophrenia. However, our study is not in accordance with meta-analysis results of Stubbs et al. (2015).

Pain is a multifaceted phenomenon, with sensory-discriminative and motivational-affective aspects. In this study the lack of difference in pain threshold between patients and controls may indicate an absence of dysfunction in the sensory-discriminative pathway of pain in patients with schizophrenia. Tolerance to pain is a more active condition, which may involve the motivational-affective pathway. This pathway is probably disrupted in schizophrenia, since negative symptoms are some cardinal symptoms of this disease (Evans et al., 2015). Therefore, patients with schizophrenia, who are usually unmotivated, are likely to have had a tendency to quickly interrupt the experience, which resulted in lower pain tolerance scores.

It was reported that patients with schizophrenia tended to avoid high-effort options in objective tests of effort-based decision-making (Salamone et al., 2016). In addition, our results could be due to the specific context of our experiment and our patients. In fact it has been suggested that a lot of factors could impact perception studies, such as age, gender, educational level, intelligence and the ability of introspection (Hall and Stride, 1954). In our study, despite patients and healthy subjects having been of a similar age, they were not matched by, for example, educational level, gender, and cognitive functions.

Looking at the results for the impact of motivation on pain, reward had a significant effect in both patients and controls, with higher pain threshold and pain tolerance when the participants were rewarded, in comparison with unrewarded participants. Interestingly, the impact of reward on pain tolerance (increase) was higher in patients with schizophrenia compared to controls.

Finally, when participants were not rewarded, pain tolerance was significantly lower in patients than in healthy subjects. However, when they were rewarded, the difference was not significant. Several hypotheses may explain these results.