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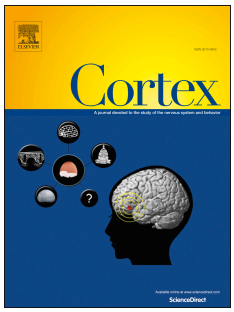

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Your misery is no longer my pleasure: Reduced schadenfreude in Huntington's disease families

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Abstract

Schadenfreude –pleasure at others' misfortunes– has been systematically related to ventral striatum activity. This brain region is affected early in individuals with manifest and pre-manifest Huntington's disease (HD). However, the experience of schadenfreude has not yet been investigated in HD. In this study, 21 manifest HD patients, 19 first-degree asymptomatic relatives, and 23 healthy controls performed an experimental task designed to trigger schadenfreude, envy (another social emotion acting as an affective control condition), and control situations. Both HD patients and first-degree relatives experienced lower schadenfreude in response to others' misfortunes, with no group differences in ratings of envy and control conditions. These results offer unprecedented evidence of a highly specific impairment in reward processing, extending previous reports in manifest and pre-manifest HD individuals. Moreover, these findings suggest that early striatal impairments may be related to reduced feelings of schadenfreude. In sum, our work contributes to the understanding of emotional impairments in early stages of HD, while shedding light on their neural correlates.

Keywords: Huntington's disease, first-degree asymptomatic relatives, schadenfreude, envy, social emotions.

1. Introduction

Schadenfreude refers to the perceiver's experience of pleasure at another's misfortune (Heider, 1958). This is a multidetermined emotion considered harmful to social relations (Cikara & Fiske, 2013). Schadenfreude can be evoked by both hostile feelings and by envy (van Dijk, Ouwerkerk, Goslinga, Nieweg, & Gallucci, 2006). Thus, the presence of the

latter emotion increases the probability of experiencing schadenfreude (Cikara & Fiske, 2013; Takahashi et al., 2009).

At the neuroanatomical level, feelings of schadenfreude have been systematically related to ventral striatum activity (Cikara & Fiske, 2011; Cikara & Fiske, 2013; Takahashi et al., 2009). This brain region is affected early in individuals with manifest (Mazziotta et al., 1987; Nopoulos et al., 2010) and pre-manifest (Aylward et al., 1994; Weeks, Piccini, Harding, & Brooks, 1996; Weir, Sturrock, & Leavitt, 2011) Huntington's disease (HD). HD is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat on chromosome 4 (Conneally, 1984). This condition is classically characterized by cognitive, motor, and behavioral abnormalities associated with neuronal loss within corticostriatal circuits (Lawrence, Sahakian, & Robbins, 1998). Neuropathological and neuroimaging studies (Della Nave et al., 2010; Muhlau et al., 2007; Nopoulos et al., 2010) have revealed selective grey matter atrophy in HD, with the earliest changes progressing from the dorsolateral to the ventromedial portions of the neostriatum. At early stages, the cerebral cortex is selectively affected with early involvement of the operculum. Subsequently, progressive atrophy involves the insular, primary sensory, motor, and visual cortices, and then the primary auditory cortex. Finally, atrophy extends to the entorhinal cortex and higher order cortical regions.

Importantly, structural and functional abnormalities in the basal ganglia (Hennenlotter et al., 2004; Ille et al., 2011; Kipps, Duggins, McCusker, & Calder, 2007) and frontostriatal pathways (Joel, 2001) have been associated with social cognition impairments in HD. Therefore, this pathology is an excellent clinical model to study the role of striatal functions

in social cognitive domains (Hennenlotter et al., 2004). Moreover, social emotions, compared to basic emotions, provide a more ecological approach to investigate subtle impairments in psychiatric and neurological conditions (Baez, Garcia, & Ibanez, 2016; Baez et al., 2013; Baez & Ibanez, 2014; Baez et al., 2012; Ibanez & Manes, 2012). To date, however, no previous work has assessed the role of ventral striatum alterations in schadenfreude. This study aims to bridge such gap.

Schadenfreude is intimately related to reward mechanisms. Indeed, this emotion may involve heightened reward processing, which is supported by increased striatal engagement (Dvash, Gilam, Ben-Ze'ev, Hendler, & Shamay-Tsoory, 2010; Takahashi et al., 2009). In manifest and pre-manifest HD individuals (Enzi et al., 2012), impaired reward processing has been related to reduced activity of the ventral striatum. Moreover, a decrease in the perceived pleasant or rewarding properties of events has been reported in animal models of HD (Renoir et al., 2011). Thus, given that reward processing and striatal regions are compromised early in this disease, subjects with manifest HD could be impaired in their capacity to experience schadenfreude. Moreover, the same could be expected in asymptomatic individuals with a family history of HD. This population represents a vulnerability group with high probability of developing the disease or some unspecific related deficits (Panegyres & Goh, 2011). Crucially, as proposed by previous studies (Baez et al., 2015; Kargieman et al., 2014), vulnerability groups offer good clinical models to investigate the progress of HD and identify potential biomarkers.

Against this background, we conducted an unprecedented study on schadenfreude in manifest HD patients and their asymptomatic first-degree relatives. To trigger this emotion,

we used a modified version of a previously reported experimental task (Takahashi et al., 2009) in which unfortunate events happened to fictional individuals. Fortunate events were also included to generate envy, a social emotion related to schadenfreude (Takahashi et al., 2009). Finally, neutral situations allowed testing task comprehension and attentional engagement. We hypothesized that both HD patients and relatives would experience lower levels of schadenfreude compared to healthy controls. Also, while schadenfreude is related to activity in the ventral striatum, envy is mainly mediated by the anterior cingulate and medial prefrontal cortices activity (Takahashi et al., 2009) –regions that are compromised later or even preserved in HD (Kassubek et al., 2004; Muhlau et al., 2007). Accordingly, we expected that the latter emotion would be preserved in both HD patients and their relatives.

2. Materials and methods

2.1. Participants

Sixty-three subjects participated in this study. The first group consisted of 21 patients genetically and clinically diagnosed with HD. A second group comprised 19 relatives (descendants or siblings) of those patients. They did not present any HD symptoms, and had not been diagnosed with HD or other neuropsychiatric diseases. Although relatives did not receive genetic testing, this population represents a vulnerability group (see details in Supplementary Data). Biological (Markianos, Panas, Kalfakis, & Vassilopoulos, 2008), clinical (Dorsey, 2012), and cognitive (Baez et al., 2015; Giordani et al., 1995; Kargieman et al., 2014) factors of familial vulnerability have been reported irrespective of whether the first-degree relatives are HD mutation carriers or not. Assessing these individuals is important to understand the nature of HD and identify potential HD biomarkers.

Both groups underwent a neurological examination and were assessed using the Unified Huntington's Disease Rating Scale (UHDRS)(Siesling, van Vugt, Zwinderman, Kieburtz, & Roos, 1998). In addition, HD patients were assessed with the Physical Disability Rating Scale (PDRS)(Myers et al., 1988) (Table 1). Patients and relatives were recruited from Magdalena, Colombia, a region with a large concentration of individuals with HD (Baez et al., 2015; Kargieman et al., 2014). Patients and relatives had no history of other major neurological illnesses, psychiatric disorders, or alcohol/drug abuse.

The control group, recruited from the same region, consisted of 23 healthy participants matched in age, gender, and years of education with the other two samples (Table 1). Control subjects did not have a history of alcohol/drug abuse, HD, or other neurologic or psychiatric disorders. All participants provided written informed consent in agreement with the Helsinki declaration. The Ethics Committee of the Autonomous Caribbean University approved the study.

2.2. Instruments

2.2.3. General cognitive state

The participants' general cognitive state was assessed with the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005). All participants were also evaluated with an EF battery which included the INECO frontal screening (IFS) (Torralva, Roca, Gleichgerrcht, Lopez, & Manes, 2009). The IFS has been shown to successfully detect executive dysfunction in patients with neurological and psychiatric diseases (Baez, Ibanez, et al., 2014; Torralva et al., 2009). This test includes the following eight subtests: (1) motor programming (Luria series, "fist, edge, palm"); (2) conflicting instructions (hitting the table

once when the administrator hits it twice, or hitting it twice when the administrator hits it only once); (3) motor inhibitory control; (4) numerical working memory (backward digit span); (5) verbal working memory (months backwards); (6) spatial working memory (modified Corsi tapping test); (7) abstraction capacity (inferring the meaning of proverbs), and (8) verbal inhibitory control (modified Hayling test). The maximum possible score on the IFS is 30 points.

2.2.1. Experimental task

Based on an existing protocol (Takahashi et al., 2009), we designed an experimental task to assess levels of schadenfreude and envy. On account of the cognitive state of the HD patients, the original task was modified and the characteristics of the target person (i.e., levels of possession and self-relevance of comparison domains) were not considered in our design. In the experimental task each participant was shown a real-life photograph and a description of two target characters matched in age and gender with the participant – relevant data were obtained in a brief interview before the task.

The task comprised two experimental blocks. In the first block, participants read eight sentences describing fortunate events (e.g., winning the lottery) involving either character (four events per character). After reading each sentence, participants rated the event in terms of how much envy they felt for the character (1 = no envy, 9 = extreme envy). In the second block, participants read and reported the intensity of their pleasure (schadenfreude, 1 = no pleasure, 9 = extreme pleasure) in response to eight unfortunate events (e.g., cuckoldry caused by the character's girlfriend/boyfriend) happening to the characters (four events per character). Moreover, two neutral events (e.g., washing clothes) were included in

each block. Events were presented in pseudo-randomized order. They were selected from an initial survey conducted to validate our materials (see Supplementary Data). Results of the pilot study showed that ratings for sentences describing fortunate and unfortunate events were significantly different from those for neutral sentences. Mean values of the ratings of envy and schadenfreude were 3.72 (*SD* = 1.81) and 4.4 (*SD* = 2.18), respectively. The mean rating for neutral events was 1.29 (*SD* = 0.68).

2.3. Data analysis

Demographic and cognitive state data were compared among groups using ANOVA and Tukey's HSD post-hoc tests. Chi square tests were applied to analyze categorical variables (gender). Ratings of schadenfreude and envy were analyzed via one-way ANOVAs. Tukey's HSD post-hoc tests were used when appropriate. To control for the influence of general cognitive status on the experimental task, we applied ANCOVA tests adjusted independently for MOCA and IFS total scores. As in other reports of neurodegenerative conditions of our group (Baez, Kanske, et al., 2016; Baez, Manes, et al., 2014; Baez, Morales, et al., 2016; Sedeño et al., 2016), only those effects that remained significant after covariation are reported. Moreover, in order to explore the relationship between executive functions, envy, and schadenfreude, we performed correlation analyses between global IFS scores and social emotion ratings for each group independently. Effect sizes were calculated through partial eta squared (η^2).

3. Results

3.1. General cognitive state

Significant differences among groups were observed in the total MOCA score ($F(2,61)=17.60$, $p<0.01$, $\eta^2=0.36$). A post-hoc analysis (Tukey's HSD, MS=21.14, df=61) revealed that HD patients were outperformed by relatives ($p<0.01$) and controls ($p<0.01$). Significant differences among groups were also observed on the total IFS score ($F(2,61)=35.01$, $p<0.01$, $\eta^2=0.53$). A post-hoc analysis (Tukey's HSD, MS=12.39, df=61) showed that HD patients had a poorer performance than relatives ($p<0.01$) and controls ($p<0.01$). A detailed analysis of scores in the IFS subscales revealed that HD patients were outperformed by controls in all executive measures, while relatives showed lower scores than controls only in the backward digit span task (see Table 1).

3.2. Schadenfreude and envy

For HD patients, the mean value of envy ratings was 3.8 (*SD* = 2.0) and the mean value of schadenfreude ratings was 3.3 (*SD* = 1.2). For relatives, the mean values of envy and schadenfreude ratings were 3.6 (*SD* = 2.1) and 3.1 (*SD* = 1.9) respectively. For controls, the mean of envy ratings was 3.0 (*SD* = 2.9) and the mean of schadenfreude ratings was 5.4 (*SD* = 2.0).

No differences among groups were observed in ratings of envy ($F(2,61)=1.57$, $p=0.21$, $\eta2=0.04$) or ratings for neutral situations ($F(2,61)=1.49$, $p=0.23$, $\eta2=0.04$). However, there were significant differences in schadenfreude ratings ($F(2,61)=21.30$, $p<0.001$, $\eta^2=0.41$). A post-hoc analysis (Tukey's HSD, MS=2.88, df=61) revealed that HD patients ($p<0.001$) and relatives ($p<0.001$) showed lower schadenfreude ratings than controls. No significant differences were observed between HD patients and relatives ($p=0.3$) (Figure 1).

Correlation analyses between envy ratings and global IFS scores showed no significant associations in any group (HD patients: r = -0.31, p = 0.16; relatives: r = -0.39, p = 0.09; controls: r = 0.27, p = 0.18). Neither schadenfreude ratings correlated with global IFS scores in any group (HD patients: r = -0.09, p = 0.67; relatives: r = -0.36, p = 0.12; controls: r = 0.15, p = 0.47).

4. Discussion

This is the first study investigating schadenfreude and envy in HD patients and their first-degree relatives. As expected, we found that schadenfreude was selectively reduced in both HD patients and relatives, while envy remained unimpaired. Our results illuminate social emotion impairments in HD and may have important clinical implications.

4.1. Schadenfreude and envy

Compared to controls, both HD patients and first-degree relatives exhibited lower schadenfreude in response to others' misfortunes. This could reflect well-established impairments in reward processing, shared by individuals with manifest and pre-manifest HD (Enzi et al., 2012). In the same vein, animal models (Renoir et al., 2011) have shown that HD mice exhibit reduced reactivity to reward, as evidenced by a decreased preference for saccharin solutions. Schadenfreude represents a rewarding feeling derived from another's misfortune. Evidence of activations of reward system areas (Cikara & Fiske, 2013; Takahashi et al., 2009) (i.e., the ventral striatum) during schadenfreude further reinforces the rewarding nature of this emotion.

The ventral striatum exhibits early compromise in subjects with both manifest (Mazziotta et

al., 1987; Nopoulos et al., 2010) and pre-manifest (Aylward et al., 1994; Weeks, Piccini, Harding, & Brooks, 1996; Weir, Sturrock, & Leavitt, 2011) HD. Our findings suggest that a highly specific social emotion impairment in those populations could be directly linked to reward system impairments following early damage to the ventral striatum. Previous studies suggest that basal ganglia abnormalities in HD are associated with multiple impairments, including motor (Thompson et al., 1988), linguistic (Kargieman et al., 2014; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005), socio-cognitive (Aviezer et al., 2009; Baez et al., 2015), and other high-order (Lawrence et al., 1996) deficits. Our results suggest that striatal abnormalities observed in HD patients and first-degree relatives may also affect the experience of schadenfreude. Moreover, degeneration of direct and indirect pathways arising from the striatum leads to impaired functioning of motor, cognitive, and affective circuits (Joel, 2001) in HD patients. Thus, abnormal schadenfreude may be better understood in terms of cortico-striatal network disruptions. Increasing evidence (e.g., Unschuld et al., 2012; Wolf et al., 2008) shows that cognitive and affective deficits in HD involve abnormal connectivity between the basal ganglia and cortical hubs. Further studies should explore the relationship between functional connectivity within cortico-striatal networks and the experience of schadenfreude in HD patients and asymptomatic first-degree relatives.

In addition, the experience of schadenfreude implies various mechanisms and may be associated to diverse cognitive processes impaired in HD. For instance, executive functions are required to properly perform tasks tapping emotional and social cognition domains (Pessoa, 2008; Uekermann et al., 2010). Emotional processing requires holding stimulus-relevant information in working memory while irrelevant information is inhibited. These

executive processes may be affected in HD patients (Lawrence et al., 1996) and asymptomatic carriers (Verny et al., 2007). However, our results showed that reduced schadenfreude is not related to executive dysfunction. Future studies should further assess the relationship between executive functions and social emotions in HD. Schadenfreude may also be linked to counterfactual thinking –generating thoughts about alternatives to past events, actions and outcomes (Bault, Coricelli, & Rustichini, 2008). Social emotions, such as schadenfreude and envy, may involve reflecting on decisions that we could have made and chose not to make, but which were adopted by someone else, thereby providing information on the outcome of choices of the other person (Coricelli & Rustichini, 2010; van de Ven & Zeelenberg, 2015). Counterfactual thinking is also impaired in HD patients (Solca et al., 2015), which may be related to the reduction of schadenfreude reported herein. Further experimental studies are needed to understand the specific relationship between schadenfreude and counterfactual cognition in manifest and pre-manifest HD patients.

Ratings of envy were similar among HD patients, relatives, and controls. This aligns with evidence that envy critically involves activations over ventral prefrontal areas, in particular the anterior cingulate cortex (Dvash et al., 2010; Takahashi et al., 2009). Neuroimaging studies have shown that gray matter in these areas is preserved in HD patients (Kassubek et al., 2004; Muhlau et al., 2007). Furthermore, contrary to schadenfreude, envy is an unrewarding emotion that involves feelings of discontent in the face of another person's good fortune. The differential pattern we observed arguably reflects the distinct nature and neural basis of schadenfreude relative to envy. The preservation of this closely related emotion support the distinctiveness of schadenfreude impairments following early brain atrophy in hubs of the reward systems.

Future studies should confirm and extend these unprecedented findings. As in other reports including vulnerable HD populations (Baez et al., 2015; Kargieman et al., 2014), the relatives assessed here did not receive genetic testing. Thus, the sample may have included both genetic pre-symptomatic individuals and healthy relatives without genetic HD heredity. Nevertheless, note that biological (Markianos et al., 2008), clinical (Dorsey, 2012; Robins Wahlin et al., 2000), and cognitive (Giordani et al., 1995; Kargieman et al., 2014) factors of familial vulnerability have been reported irrespective of whether the first-degree relatives were HD mutation carriers or not. For instance, healthy individuals at risk for HD (Giordani et al., 1995), regardless of their HD gene status, may exhibit low performance in some neuropsychological measures. Consistent with recent studies (Baez et al., 2015; Kargieman et al., 2014), our results showed that although the relatives group assessed here might include both HD gene carriers and non-carriers, its performance on social emotion tasks was significantly different from that of controls. Thus, they can reasonably be framed as a vulnerability group at risk of developing HD. Assessing these individuals is important to understand the nature of HD and identify potential biomarkers. Future studies should further assess social emotions in first-degree relatives with and without the HD mutation.

The selective reduction of schadenfreude in HD patients and relatives may conceivably be related to a general impairment in reward processing (Enzi et al., 2012). As we did not include a more general measure of this domain, future investigations in HD should aim to disentangle the relative contribution of specific vs. global impairments in reward processing. Furthermore, considering that such general impairments in HD may impact on classical (e.g., decision making) and non-classical (e.g., schadenfreude experience,

anhedonia symptoms) cognitive and affective domains, further studies should adopt a multidimensional approach to understand such alterations. In addition, further research should employ structural and functional neuroimaging methods to explore brain abnormalities in HD patients or relatives, and their relationship with reward processing. Further volumetric and fMRI studies may provide additional insights about the specific relationship among structural and functional changes in the ventral striatum and associated schadenfreude deficits.

Our findings may also have important clinical implications. Social emotions such as schadenfreude and envy have not been previously studied in HD. The present findings suggest that processing of social emotions may be included in the clinical assessment of HD patients or asymptomatic relatives. Given that facial emotion recognition has been proposed as a sensitive marker of disease onset and progression in HD (e.g., Paulsen et al., 2006; Tabrizi et al., 2009), our results suggest that processing of social emotions may also constitute a potential marker of HD onset or vulnerability. Large-scale longitudinal studies are required to test this possibility. Moreover, our results indicate the existence of a possible link between the diminished capacity to experience schadenfreude and reward processing, which are probably related to relevant clinical symptoms of HD (i.e., anhedonia). Reward processing impairments may be a dimensional symptom underlying various clinical features of HD. For instance, reward may be related to both anhedonia and specific social cognition impairments, as well as social disinterest and lack of pleasure from social contact. Future studies should explore the specific relationship between reward, anhedonia, and social cognition in HD patients, with a view to designing more effective treatments.

4.2. Conclusion

The findings of this exploratory study showed that the malicious pleasure of schadenfreude is selectively reduced in HD patients and asymptomatic first-degree relatives, opening a new field of research regarding reward processing, social emotions, and neurodegeneration. Our findings open the door to future studies investigating social emotion processing in other clinical populations characterized by striatal impairments (e.g., Parkinson's disease and schizophrenia). This particular knowledge might have important implications for clinical and therapeutic interventions.

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Figure Legend

Figure 1. Schadenfreude and envy ratings. HD patients and relatives showed lower schadenfreude ratings than controls. No differences were observed in envy or neutral ratings. Boxes represent median and interquartile range values, and whiskers indicate the minimum and maximum values.

Table 1. Demographic, clinical and executive functions assessments.

		HD (n=21) Mean(SD)	REL (n=19) Mean(SD)	CTR (n=24) Mean(SD)	HD vs CTR	REL vs CTR
Demographics	Age (years)	45.0 (10.1)	37.7 (17.2)	40.0 (14.7)	NS	NS
	Gender (F:M)	12:9	12:7	12:12	NS	NS
	Education (years)	7.0 (2.3)	6.5 (2.2)	6.1 (2.7)	NS	NS
Clinical assessment	UHDRS	22.0 (9.6)	1.8 (2.2)			
	PDRS	73.8 (14.9)	99.4 (2.2)			
Cognitive assessment	MOCA total score	15.7 (5.9)	23.6 (3.7)	22.2 (3.8)	0.0001	NS
	IFS Total Score	14.5 (5.1)	20.1 (2.8)	22.0 (1.9)	0.001	NS
	Motor series	1.9 (0.7)	2.7 (0.5)	2.8 (0.4)	0.0002	NS
	Conflicting instructions	1.5 (0.8)	2.8 (0.3)	2.7 (0.4)	0.0001	NS
	Go- no go	0.9 (0.7)	2.0 (0.7)	2.3 (0.5)	0.0001	NS
	Backward digits span	2.0 (0.9)	2.8 (0.9)	3.5 (0.5)	0.0001	0.02
	Verbal Working memory	0.9 (0.5)	1.3 (0.4)	1.5 (0.5)	0.0004	NS
	Spatial working memory	1.6 (0.9)	2.4 (0.6)	2.3 (0.4)	0.001	NS
	Abstraction capacity	1.4 (0.9)	2.0 (0.8)	2.5 (0.6)	0.0002	NS
	Verbal inhibitory control	2.7 (1.3)	3.7 (0.9)	4.0 (0.9)	0.0004	NS

HD=Huntington's disease patients; REL=Asymptomatic relatives; UHDRS=Unified Huntington's Disease Rating Scale; PDRS=Physical Disability Rating Scale total functional capacity scale; MOCA=Montreal Cognitive Assessment; IFS=INECO frontal screening.