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Timing matters: Endogenous cortisol mediates benefits from early-day psychotherapy

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ABSTRACT

Objective: No simple way to augment fear extinction has been established. Cortisol has shown to enhance memory extinction and preliminary evidence suggest that extinction learning maybe more successful in the morning when cortisol is high. The aim was to determine whether exposure sessions conducted earlier in the day are associated with superior therapeutic gains in extinction-based psychotherapy. We also examined the role of cortisol levels as a mediator between time of day and therapeutic gains.
Method: Participants were 24 individuals meeting DSM-IV criteria for panic disorder with agoraphobia. Participants received 3 weekly in-vivo exposure sessions, yielding 72 total sessions for analysis of time of day effects. Session start times were evenly distributed across the day. The outcome measures were reductions in panic symptom severity (avoidance behaviors, threat misappraisal, perceived control, and panic disorder symptom severity).
Results: Sessions starting earlier in the day were associated with superior therapeutic gains by the next therapy session. Earlier sessions were also associated with higher pre-exposure cortisol levels, which in turn were related to greater clinical improvement by the next session. Cortisol thus was found to mediate the effect of time of day on subsequent outcome, providing a link between earlier exposure sessions and greater clinical improvement.
Conclusion: The data suggest that early-day extinction-based therapy sessions yield better outcomes than later-day sessions, partly due to the enhancing effect of higher cortisol levels.

1. Introduction

Exposure therapy – systematic and controlled confrontation with feared situations or sensations – facilitates fear extinction through acquisition of new, fear-discordant information (Bouton, 2002; Milad et al., 2006). Therapeutic success of exposure therapy for fear-based avoidance is well-established treatment for anxiety disorders (McNally, 2007). However, a significant number of patients experience limited recovery or a return of fear following exposure (Meuret et al., 2012a; Loerinc et al., 2015). Identification of moderators and mediators that can facilitate corrective learning is of great scientific and clinical interest (Hermans et al., 2006; Graham and Milad, 2011). However, few if any reliable ways of enhancing treatment outcome exist (Schneider et al., 2015; for a review), and no "simple" determinant of enhanced learning has been identified. Both psychophysiological and contextual indices of extinction, such as fear reactivity (activation, within- and between-session habituation of fear levels) and exposure characteristics (variation of stimulus, session spacing and duration), show varying results (Meuret et al., 2012b; Craske et al., 2008, for a review).

One biological factor associated with enhanced extinction learning is cortisol. Research over the last decades has provided growing evidence for a beneficial effect of glucocorticoids on extinction learning. A dual mechanism is assumed by which cortisol reduces the retrieval of aversive memories, and thereby partially interrupts the vicious cycle of spontaneous retrieving, re-experiencing and (re)consolidating of aversive memories, while simultaneously enhances fear extinction by means of facilitating the storage of corrective experiences. The latter process is thought to be active in exposure techniques taught in cognitive-behavioral therapy (de Quervain et al., 2009; review). In recent findings from laboratory-based exposure protocols show that higher levels of cortisol (exogenous and endogenous) during exposure sessions are linked

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to lower, concurrent stimulus-induced fear and enhanced approach behaviors (Soravia et al., 2006, 2014; de Quervain et al., 2011 Lass-Hannemann and Michael, 2014), and to attenuated negative emotional arousal during and following response to acute stress (Het et al., 2012). The observed "fear-buffering" effects of cortisol have been ascribed to the ability of glucocorticoids to inhibit the retrieval of aversive memories, while simultaneously enhancing extinction learning (Roozendaal et al., 2006; Bentz et al., 2010; de Quervain et al., 2009). Two naturalistic exposure studies further documented cortisol-related enhancement of extinction learning, but without direct links between cortisol and concurrent fear levels. Siegmund et al. (2011) showed greater clinical improvements (trend level) in panic patients with higher cortisol levels undergoing in-vivo exposure. Higher cortisol levels during exposures were also associated with enhanced clinical improvement in a multi-session in-vivo exposure protocol for panic disorder and agoraphobia (Meuret et al., 2015). In the latter study, greater cortisol awakening responses on exposure day also predicted treatment gains. A potential link between time of treatment session and treatment gains was not examined in those analyses, but if higher cortisol enhances the beneficial impact of exposure treatment, and normal diurnal variation in cortisol levels produces the highest levels in the morning, morning sessions may be advantageous.

The diurnal rhythm of cortisol is well established (Kirschbaum and Hellhammer, 1989), with a morning peak followed by a steady decline throughout day, and a nadir in the evening. While the function of the acute rise in cortisol triggered by morning awakening remains undetermined, the rise is thought to facilitate performance and orientation to the day's upcoming demands (Fries et al., 2009; Chida and Steptoe, 2009). Indeed, preliminary evidence supports the link between circadian factors, cortisol, and extinction learning. Using a fear conditioning and extinction paradigm in healthy young adult males, Pace-Schott and colleagues demonstrated enhanced extinction learning in participants assigned to the "morning" (7–10 a.m.) versus "evening" group (7–10 p.m). The evening group had significantly lower salivary cortisol levels at time of training than the morning group (Pace-Schott et al., 2013), but the investigators did not perform a mediation analysis to determine if cortisol mediatedthe superior morning results. Furthermore, spider-phobic adults assigned to receive a single-session laboratory-based exposure at 8 a.m. (versus 8 p.m.), had higher cortisol levels during the exposure and showed greater approach behavior and a trend toward lower subjective fear of spiders at post-treatment and 3-months later (Lass-Hennemann and Michael, 2014). Again, no mediation analysis was undertaken.

These early findings may give rise to a simple, clinical hypothesis: exposure sessions are most effective in the morning, since the higher cortisol in the morning will maximize memory consolidation of new information and hence ultimately lead to better clinical outcomes. It is notable that time-of-day recommendations are common standard for psychotropic drug treatment, largely due to the handling of side-effects. However, such recommendations have not yet been explored for psychotherapy treatment. Though intriguing, the existing evidence for optimal exposure session timing is still modest and prior designs have not allowed for the direct testing of cortisol as a mediator of the time-of-day effects, to determine whether greater cortisol levels, independent of time-of-day, are responsible for improved clinical outcomes, or conversely, whether time-of-day enhances fear-learning independent of cortisol level. Sorting out the contributing factors may allow us to more optimally design exposure exercises.

Here we examined the role of time-of-day as a simple and practical predictor of therapeutic gains from exposure, examining patients undergoing multi-session in-vivo exposure therapy for panic disorder and agoraphobia. Using a cross-lagged analytic approach, we were also able to examine the role of cortisol levels as a mediator between time of day and therapeutic gains, hypothesizing that exposure sessions performed earlier in the day would result in greater clinical benefits, mediated by the enhancing effects of the higher levels of cortisol usually seen in the earlier part of the day.

2. Methods

2.1. Participants

Data came from a prior study that examined psychophysiological predictors of exposure treatment outcomes (Meuret et al., 2012b). Twenty-four outpatients with Panic Disorder (PD) with agoraphobia were recruited through an academic clinic and local advertisements. Patients were primarily white (95.8%), female (87.5%), married (n = 45.8%), well educated (M = 15.7 years, SD = 2.4), and employed (75.0%). The mean age was 32.4 years (SD = 9.1). Inclusion criteria were current principal diagnosis of PD and agoraphobia, age 18–65, on a stable dose of psychotropic medication for at least three months prior to study initiation (if applicable), and agreement not to initiate additional therapy (or change medication) until after the two-month follow-up. Exclusion criteria were major medical illness, pregnancy or lactation, suicidality, psychotic or bipolar disorder, drug abuse or dependence.

Fifty-four percent of the patients had at least one additional current DSM-IV Axis I diagnosis (generalized anxiety disorder [53.8%], social anxiety disorder [15.4%], post-traumatic stress disorder [15.4%], specific phobia [15.4%], anxiety disorder NOS [7.7%]) and/or mood disorder (dysthymic disorder [23.1%], mood disorder NOS [7.7%]). Additionally, 41.7% had met diagnostic criteria for at least one major depressive episode in the past. Structured clinical interviews for DSM-IV (First et al., 1995) confirmed diagnoses, with high inter-rater reliability for PD (κ = 1.00), and comorbid diagnoses (κ = 0.93). Based on the agoraphobic avoidance item (Item 4) of the Panic Disorder Severity Scale (PDSS; Shear et al., 1997), the majority presented with avoidance behaviors in the moderate to severe range (8.3% extreme, 58.3% severe, 29.2% moderate, and 4.2% mild range). The majority of patients were taking a stable dose of psychotropic medication (62.5%) (antidepressants [33.3%], benzodiazepines [41.7%], beta-blockers [4.2%], anticonvulsants [4.2%], with 16.7% taking more than one type). The study was approved by local institutional review boards and written informed consent was obtained from all participants.

2.2. Exposure therapy

In-vivo exposure therapy was comprised of three weekly sessions plus a fourth session at two-month follow-up (2 MFU) (see Meuret et al., 2012b for more details). Patients were asked to select the highest ranked situation that they could enter and endure from their fear and avoidance hierarchies. No upper time-limit was set on duration; rather patients were asked to stay in the situation until they no longer appraised the situation as threatening (expectancy violation). A minimum duration of at least 30 min was encouraged. Exposure situations included highways and overpasses, tall buildings, public transportation (subways and intercity trains, boats), public places (supermarkets, movie theatres, lecture halls), or enclosed places (small closets, elevators) or crowds. Contextual features were purposefully varied across exposures (e.g., different highways, session durations, with/without therapist) to enhance inhibitory learning and ensure a generalization effect (e.g., Craske et al., 2008). Our time-of-day analyses presented here focus on the weekly exposures (session 1–3, excluding the 4th exposure which took place 2 months later) to capture the week to week effects of time and cortisol. Patients completed 68 out of 72