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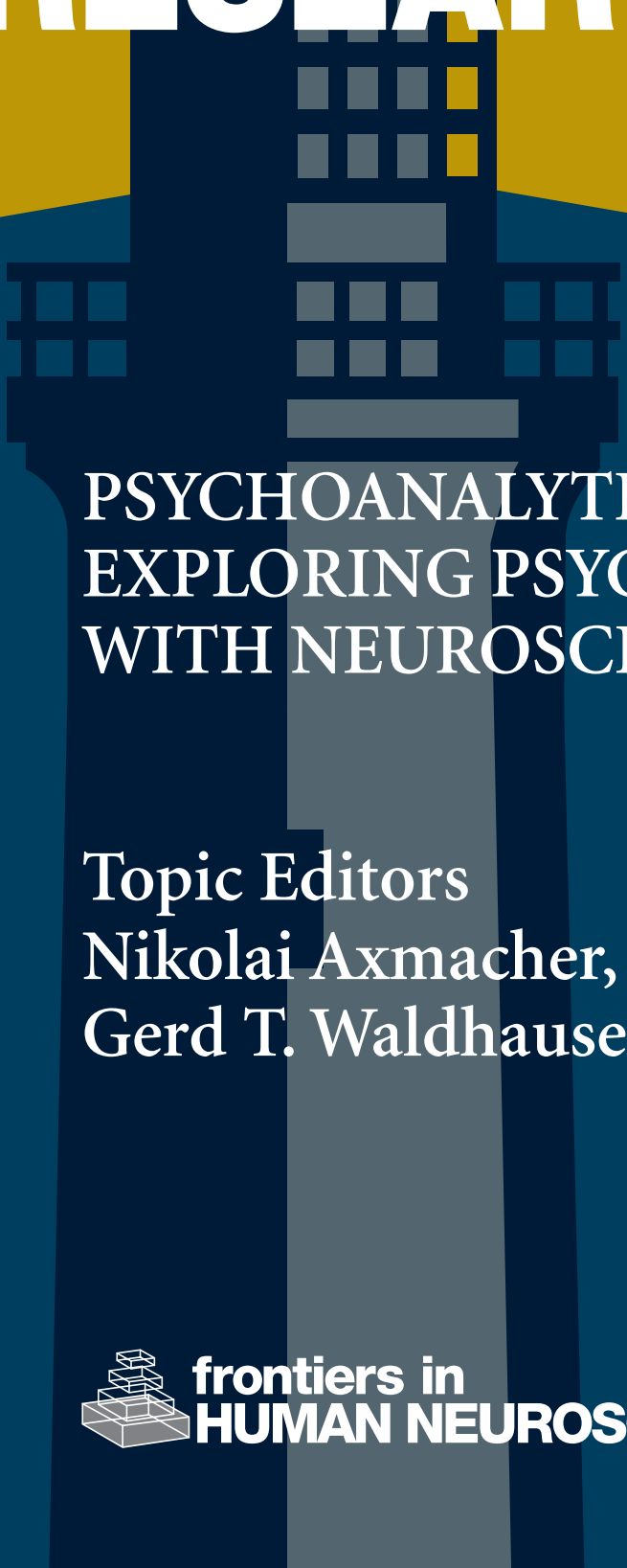

# PSYCHOANALYTICAL NEUROSCIENCE: EXPLORING PSYCHOANALYTIC CONCEPTS WITH NEUROSCIENTIFIC METHODS

Topic Editors
Nikolai Axmacher, Henrik Kessler and
Gerd T. Waldhauser

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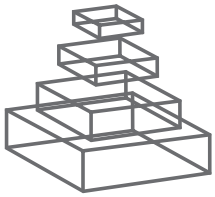

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# PSYCHOANALYTICAL NEUROSCIENCE: EXPLORING PSYCHOANALYTIC CONCEPTS WITH NEUROSCIENTIFIC METHODS

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EDITORIAL
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# Editorial on psychoanalytical neuroscience: exploring psychoanalytic concepts with neuroscientific methods

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**Keywords: psychoanalysis, neuroscience, neuropsychoanalysis, psychodynamic psychotherapy, neuroimaging**

The Research Topic "Psychoanalytical neuroscience: Exploring psychoanalytic concepts with neuroscientific methods" was cross-linked in two Frontiers journals, *Frontiers in Human Neuroscience* and *Frontiers in Psychoanalysis and Neuropsychoanalysis*. Thus, contributing authors could choose to submit to either of those two journals. Among the 16 finally accepted contributions, 14 were submitted to *Frontiers in Human Neuroscience* and 2 to *Frontiers in Psychoanalysis and Neuropsychoanalysis* (potentially related to the fact that during the time of submission only the former journal was listed with an impact factor; this has changed by now). These articles covered a wide range of topics, from empirical studies on basic psychoanalytic concepts ($n = 4$) to articles on the neurobiological mechanisms of psychodynamic therapy ($n = 3$) and theoretical reviews ($n = 9$).

Studies from the first group investigated the empirical basis of specific psychoanalytic concepts such as repression (using fMRI; Kehyayan et al., 2013), unconscious conflict (using EEG; Shevrin et al., 2013), dreams (using questionnaires; Mota-Rolim et al., 2013) or personality structure related to depression (using fMRI; Taubner et al., 2013). Studies from the second group adopted a broader, more clinical perspective and explored neuronal changes during psychodynamic therapy. Therapy involves various complex changes in psychical structure. Among those, articles in the Research Topic mainly reported on therapy-induced reductions of defenses (Buchheim et al., 2013; de Greck et al., 2013) and changes in dream content (Fischmann et al., 2013). These two approaches—studies on psychoanalytic concepts and on psychotherapy effects—have already led to interesting convergences: For example, de Greck et al. (2013) described a normalization of initially reduced activity of the medial temporal lobe after psychodynamic therapy in patients with somatoform disorders; the same region was found to be inhibited in an experimental model of repression (Schmeing et al., 2013). We believe that in the future, it will remain necessary to combine these two approaches in order to link psychoanalysis—which is before all a very specific clinical intervention—with experimental neuroscientific research.

In addition to empirical work, the Research Topic includes various theoretical articles. One repeating theme among them was the relevance of using individualized stimuli to allow for a neuroscientific investigation of subjective "meaning" that is central to psychodynamic approaches (Boeker et al., 2013; Kessler et al., 2013; Cusumano and Raz, 2014). Other topics involved the investigation of unconscious memory processes (Ruby, 2013) and the combination of psychotherapy with EEG neurofeedback (Unterrainer et al., 2013). Further theoretical accounts included a psychoanalytic framework of addiction (Johnson, 2013), a neurobiological theory of the Lacanian concept of jouissance (Bazan and Detandt, 2013), considerations of a potential relationship between microglia and the Freudian "death drive" (Kato and Kanba, 2013), and a review on the use of psychedelic drugs to examine psychoanalytic concepts (Carhart-Harris et al., 2014).

All authors were asked to elaborate on their view of the potential benefit of linking psychoanalysis and neuroscience, which was formulated by the following questions: "*First, from the neuroscientific side, why should researchers in the neurosciences address psychoanalytic ideas, and what is (or will be) the impact of this connection on current neuroscientific theories? Second, from the psychoanalytic side, why should psychoanalysts care about neuroscientific studies, and (how) can current psychoanalytical theory and practice benefit from their results?*" As expected, authors responded differently to this question. Some argued that addressing psychoanalytic concepts is beneficial to advance neuroscientific research: It may allow for an explanation of results which are otherwise difficult to interpret, and enhance the realm of processes that can be investigated using neuroscientific methods (Kehyayan et al., 2013; Ruby, 2013)—in particular, personal meaning (Boeker et al., 2013; Kessler et al., 2013; Shevrin et al., 2013; Cusumano and Raz, 2014). Others suggest psychoanalysis as a useful framework to better understand, prevent and treat psychiatric diseases such as addiction (Johnson, 2013) or depression (Taubner et al., 2013).

Other authors argued that psychoanalysis could also benefit from neuroscientific research. A relatively direct link was described by Unterrainer et al. (2013), who suggested that a combination of neurofeedback with psychodynamic psychotherapy is more beneficial than either treatment alone. On a more theoretical level, results from neuroimaging studies on psychotherapeutic treatment may allow one to disentangle the complex processes during psychotherapy, by relating the brain activation patterns to results from previous experimental studies—for example, linking them to previous research on interpersonal attachment (Buchheim et al., 2013), self-related processing (Fischmann et al., 2013), or emotional memory (de Greck et al., 2013). Although such reverse inference has been criticized due to the lack of specificity of neural activation patterns, its

viability can be formally tested (Poldrack, 2011; Hutzler, 2014). Furthermore, neuroscience research may break down complex psychoanalytic concepts into biological processes that are easier to grasp: Carhart-Harris et al. (2014) proposed that application of psychedelic drugs during neuroimaging allows for an experimental investigation of primary process thinking, and Bazan and Detandt (2013) and Kato and Kanba (2013) suggested that neuroscientific findings would help to better understand complex psychoanalytic concepts such as jouissance and the death drive, respectively. The resulting integrated neuro-psychoanalytic concepts may then contribute to the development of a new metapsychology based on current neuroscientific knowledge.

We were glad to learn that our Research Topic raised considerable interest. This is not only reflected in the relatively high number of contributions; in addition, one of the authors (NA) was pleased to see it summarized in a presentation at the annual International Neuropsychoanalysis Congress in New York City by Mark Fisher entitled "*Toward a neuroscience theory of psychoanalysis: open road or dead end?*". We believe the articles in this topic are good evidence that the emerging field of psychoanalytical neuroscience is an open road rather than a dead end: While psychoanalysis allows neuroscientific researchers to embrace the full complexity of human subjective experience and its determination by unconscious conflicts, results from the neurosciences may eventually provide psychoanalysis with a new metapsychological framework. Much work remains to be done down the road, though.

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REVIEW ARTICLE
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# Essentials of psychoanalytic process and change: how can we investigate the neural effects of psychodynamic psychotherapy in individualized neuro-imaging?

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The paper focuses on the essentials of psychoanalytic process and change and the question of how the neural correlates and mechanisms of psychodynamic psychotherapy can be investigated. The psychoanalytic approach aims at enabling the patient to "remember, repeat, and work through" concerning explicit memory. Moreover, the relationship between analyst and patient establishes a new affective configuration which enables a reconstruction of the implicit memory. If psychic change can be achieved it corresponds to neuronal transformation. Individualized neuro-imaging requires controlling and measuring of variables that must be defined. Two main methodological problems can be distinguished: the design problem addresses the issue of how to account for functionally related variables in an experimentally independent way. The translation problem raises the question of how to bridge the gaps between different levels of the concepts presupposed in individualized neuro-imaging (e.g., the personal level of the therapist and the client, the neural level of the brain). An overview of individualized paradigms, which have been used until now is given, including Operationalized Psychodynamic Diagnosis (OPD-2) and the Maladaptive Interpersonal Patterns Q-Start (MIPQS). The development of a new paradigm that will be used in fMRI experiments, the "Interpersonal Relationship Picture Set" (IRPS), is described. Further perspectives and limitations of this new approach concerning the design and the translation problem are discussed.

**Keywords: psychoanalytic process, psychodynamic psychotherapy, individualized neuro-imaging, design problem, translation problem, Interpersonal Relationship Picture Set (IRPS), Operationalized Psychodynamic Diagnosis (OPD-2)**

## INTRODUCTION

### NEUROBIOLOGICAL STUDIES OF PSYCHOTHERAPY

The recently emerged dialog between psychoanalysis and neuroscience (Shevrin et al., 1992; Solms et al., 1998; Kandel, 1999; Beutel et al., 2003; Northoff, 2007; Northoff et al., 2007) led to several empirical hypotheses and investigations of psychodynamic concepts like defense mechanisms (Shevrin et al., 2002; Boeker et al., 2006; Northoff, 2007), self (Milrod, 2002), memories (Gabbard, 2000; Mancia, 2006; Peres et al., 2008), dreams (Solms, 1995, 2000; Andrade, 2007), empathy (Gallese et al., 2007). While these originally psychodynamic concepts are currently investigated in the neuroscientific context, the neural basis of core elements of psychoanalysis and psychodynamic psychotherapy has not been elucidated yet.

Though neurobiological changes in some single cases undergoing psychodynamic psychotherapy have been reported (Viinamäki et al., 1998; Overbeck et al., 2004; Saarinen et al., 2005; Lai et al., 2007; Lehto et al., 2008; Kessler et al., 2011a, 2012), systematic and well-controlled brain imaging studies of the neural effects of psychodynamic psychotherapy are still lacking.

In contrast to psychodynamic psychotherapy, the neural effects of other forms of psychotherapy like cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have been studied in brain imaging more often (see Roffman et al., 2005; Linden, 2006; Beauregard, 2007; Frewen et al., 2008; for reviews). These studies demonstrated neural modulation in various brain regions encompassing subcortical as well as medial and lateral cortical regions during predominantly cognitive-emotion regulation tasks before and after CBT or IPT. Interpretation of these findings is however constrained by various methodological problems; these include issues like objectification and quantification of the effects of psychotherapy in behavioral and subjective parameters, selection of the activation task in functional imaging, appropriate control groups, physiological, behavioral, and psychological variables indicating task-specific effects of neural stimulation, distinction between the target symptom and its possible underlying

psychodynamic processes, etc. (see Frewen et al., 2008, for a detailed discussion).

While brain imaging studies of both CBT and IPT are already confronted with numerous methodological problems, the situation is even more difficult in the case of psychodynamic psychotherapy. For instance, the therapeutic relationship, including transference and counter-transference, plays a much more essential role in psychodynamic psychotherapy than in CBT and IPT; this makes it necessary to include the client-therapist relationship as an intervening variable in neural analysis. Another problem is the conceptualization of psychodynamic phenomena like ego, defense mechanisms, etc., and their translation into psychological variables for subsequent experimental testing in functional brain imaging. The neuropsychoanalyst who wants to study the neural effects of psychodynamic psychotherapy is thus confronted with numerous and highly complex input variables that he needs to account and control in order to make reliable and valid investigations of the output, the neural effects, possible.

## ESSENTIALS OF PSYCHOANALYTIC PROCESS AND CHANGE

To this end, it is necessary to describe and characterize the essential and specific aspects that account for the process and change of a patient during a psychoanalysis or psychoanalytic psychotherapy. This could be the basis for the development of meaningful research designs and paradigms. The main questions in this respect are:

- What is the process and what is changed within a psychoanalysis or psychoanalytic psychotherapy?
- Which are the mechanisms, techniques, and actions that enable psychoanalytic process and change?

Patients mostly seek psychotherapy because of distress, i.e., they suffer from psychic symptoms, dysfunctional behaviors, and/or from disturbances in their psychosocial environment (interpersonal problems, in relationships, at work etc.) with the intention to reduce and resolve the distress. Often patients also aim to achieve a greater self-understanding. Others wish to be supported emotionally and personally or receive guidance and instructions from the therapist for resolving their problems.

The specific aspects concerning the therapeutic process and change in psychoanalysis and psychoanalytic psychotherapy address not only symptoms and dysfunctional behaviors. Another objective is to find out what may lie behind them. This is connected to the fundamental psychoanalytic concept that conscious, so-called "manifest" symptoms, thoughts and actions of the patient imply an unconscious "latent" meaning and motivation. Within a psychoanalytic perspective, conscious symptoms, and disturbances are assumed to be the result of mechanisms of defense and formations of compromise, which deal with multiple pre-conscious or unconscious factors. Such dynamics have a strong impact on how one thinks, feels, and behaves. Pre-conscious or unconscious factors may constitute intrapsychic conflicts or dilemmas, wishes, expectations, fantasies, or structural psychic functions (super-ego, ego and id, self- and object-representations, capacities to regulate affects, impulses, self-esteem, relationships with others etc.).

Consequently, a basic psychoanalytic approach to enable a therapeutic process is to generate and foster a patient's insight into and understanding of these pre-conscious or unconscious aspects and parts of him- or herself. This is to make conscious what had been unconscious before, which is part of what Freud (1933) wrote: "Where id was, there shall ego be." A fundamental psychoanalytic technique during sessions is to ask patients to report about "what comes into their heads, even if they think it is unimportant, irrelevant, or non-sensical" (Strachey, 1953), which was called by Freud "free association." Another approach is the patient's report of dreams and the associations to them.

On the psychoanalysts' part, the correspondent technical approach is a special form of listening ("evenly suspended attention"), the use of clarification and interpretation and the formulation of hypotheses on how the patient functions mentally to establish links to unconscious conflicts and aspects; something the patient cannot perceive on his/her own and/or accept as being connected with his/her conscious thinking and current-day functioning. However, against the patient's free association, the building of links with unconscious aspects and gaining insight in oneself, resistances and transference come into play—which both can build the grounds for interpretations of the analyst. The psychoanalytic approach aims at enabling the patient to "remember, repeat, and work through" (Freud, 1914) what has been experienced in the past, repressed, or internalized. Interpretation and insight may be the start of a reorganization of thoughts—the former pre-conscious may become conscious.

Psychoanalysis focuses on childhood experiences and relations with significant others (mother, father, siblings etc.). These relations had and still have an impact on a person's life. It is expressed in current relationships of the patient in the here-and-now with important persons or the analyst. Beutel (2009) summarizes effects that early childhood interpersonal experiences have on cerebral development through genetic expression and the development of neural connections.

Freud conceived the transference of the patient (so did his followers regarding the countertransference of the analyst) as obstacles to the therapy process. The adapted concepts were the start of developing the second basic approach in psychoanalysis and psychoanalytic psychotherapy: the focus is on what is happening in the therapeutic relationship on the basis of transference and countertransference. Dysfunctional, maladaptive relationship patterns, fears, and wishes of the patient tend to be repeated in the relation to the analyst. The relation toward the analyst (and the analyst itself) constitutes the groundwork for the patient's internal structure of expectations in relationships. The analytic setting fosters the evolution of these inner conceptions. Within the transference situation, unconscious processes can be actualized. Experiencing a secure attachment with the analyst the patient may be enabled to become aware and reconstruct his/her memories and relationships (that may have structured him/her) and eventually work them through.

Andrade (2005) stresses the effect of positive transference as the basis of therapeutic action. The relationship between patient and analyst promotes an identification that is based upon introjection (of a good object) and empathy and can construct a

new affective organization. According to Andrade (2005), the affective nucleus fosters cognitive development. On the other hand, interpretation—as the classic method of psychoanalysis—is related to explicit memory (as part of the cortex) only and does not effectively deal with implicit memory (as part of subcortical areas). Andrade (2005) points out that implicit memory can only be seen through repetitive transference (cf. Beutel, 2009). These implicit memories are unconscious affective structures that can be emptied of their quotas of affect through transference (Andrade, 2005). A new affective configuration can be established.

The Boston Change Process Study Group (2007) depicts early childhood memories (for example, attachment patterns within the second year of life) as implicit relation knowledge. This internal configuration constitutes the intercourse with others, which becomes evident in subsequent object relations. The Boston Change Process Study Group (2007) defines the intrapsychic as interpersonal experience that is implicitly incorporated. To link therapeutic change with neuroscience Andrade (2005) deduces that "inadequate object relations can lead to neurophysiological changes and that adequate analytic relations lead to psychic changes that correspond to neuronal changes" (p. 684). As described before, introjection may be the neurochemical basis of psychic change, since new neural circuits—as a result of the secretion of neurotransmitters—develop. Also, Beutel (2009) describes the neuronal plasticity that evolves after mechanisms of learning and their repetition. In psychotherapy, these progressions take time and need affective involvement (Beutel, 2009).

Within a psychotherapeutic environment, Sterba (1934) described the "therapeutic division of the ego" into an experiencing and an observing ego. During psychoanalysis the patient's ego is at the same time remembering or working through and also analyzing this process. The conscious, reasonable, non-neurotic parts of the patient's ego can be distinguished from the unconscious, conflict-motivated, irrational portions of the ego (Sterba, 1934). This potential of the neo-cortex (analyzing subcortical activities) may be linked to neurosciences in the way Andrade (2005) explains the difference between unconscious implicit and conscious explicit memories (cf. Beauregard, 2007).

Beutel and Huber (2008) state in their review that psychoanalysis has an effect on the brain and argue that the division of psychological psychotherapy and biological psychiatry regarding a patient's treatment has become out-dated. The authors stress that today the main theorem of psychoanalysis (a major part of psychic activity remains unconscious) is a convention in neuroscience. Within psychoanalysis, patients learn to deal with their reactivation of patterns in their transference. In this sense, the reconstruction of object-related, psychic configurations resembles the therapeutic effect Andrade (2005) explained.

From a neuroscientific perspective, the problem of showing these effects within methodical borders remains a challenge for the future. For instance, Zwiebel (2007) depicts the difficultness to fully understand the functioning of the analyst. Analysts oscillate between so-called personal and technical poles when treating their patients (Zwiebel, 2007). Thus, the therapeutic process can be understood to be on a micro-psychological level that can hardly be quantified (cf. Beutel and Huber, 2008).

## TWO METHODOLOGICAL PROBLEMS

How can the complexity of input variables be dealt with in order to enable future brain imaging studies in psychodynamic psychotherapy? The general aim of this paper is to discuss the variables that need to be controlled and measured in studying the neural effects of psychodynamic psychotherapy. We will discuss the various variables and the methodological problems which can be subsumed under two main headings, the design problem and the translation problem. The design problem addresses the issue of how to account for functionally related variables in an experimentally independent way. For instance, the activation tasks employed in brain imaging should somehow mirror and simulate those functional processes that are assumed to mediate the therapeutic effects of psychodynamic psychotherapy. Experimentally however, we need to measure and account for both variables in an independent way without any confusion between them. The translation problem raises the question of how to bridge the gaps between the different levels of the concepts presupposed in such investigation. The gap between the personal level of the therapist and the client on the one hand, and the neural level of the brain on the other, needs to be bridged. There is also a gap between the behavioral effects of psychodynamic psychotherapy the therapist can observe and the subjective effects the client himself experiences. Finally, the gap between the psychodynamic level of the psychodynamic psychotherapy, the psychological level of the activation task in brain imaging and the neural level of the parameters to be measured needs to be bridged. The development of bridges for the various gaps is crucial in developing an experimentally sound design that allows for valid and reliable measurement and interpretation of the data. We will discuss both problems here, the design problem and the translation problem in their various facets which will be illustrated by a specific example, the example of introjection (see below for exact definition).

### DESIGN PROBLEM

The design problem deals with the issue how to account for functionally related variables in an experimentally independent way. Relevant inputs that enter such study designs include the psychotherapist, the client, the therapeutic relationship and the investigator, i.e., the experimentator (See **Figure 1** and **Table 1**). This discussion of the relevant inputs will shed some light on which and how their variables can be controlled and accounted for in experimental design.

#### *The psychotherapist as "input"*

What does the psychotherapist put into psychodynamic psychotherapy? First and foremost he puts in his own personality, his cognitions, his affects, and ultimately his own life history. In the further course of the interaction between the patient and the therapist it is the psychotherapist's perspective on the patient's thoughts, feelings, and behavior which essentially contributes to the development of the therapeutic relationship. Recent research demonstrated that the psychotherapist himself, as a personality

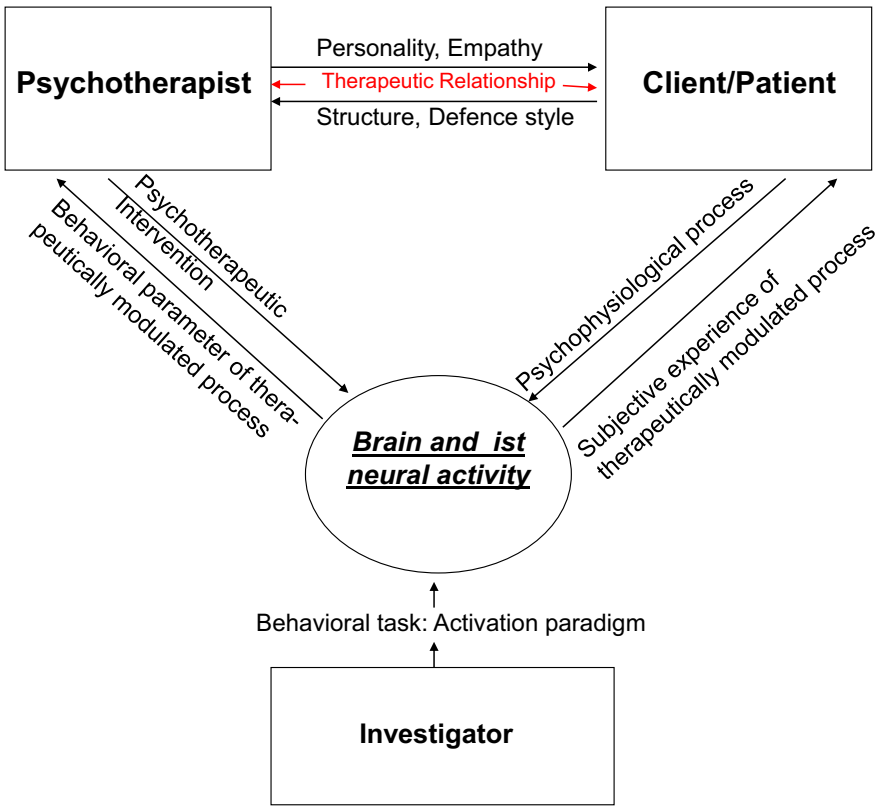


**FIGURE 1 | The design problem.**

with all his/her affects, cannot remain abstinent in psychotherapy as originally envisioned by Freud. If the patient experiences the analyst as an "impenetrable object," it can lead to serious difficulties in the analytic process, e.g., the patient will transfer his/her projections onto the therapist, which in turn can trigger unconscious "hardening" by the therapist (Skogstad, 2013). Kohut (1959) pointed out that the capacity to show empathy is a major factor in how the relationship between therapist and client can develop which in turn has a strong impact on potential therapeutic effects. A recent study investigated cognitive and emotional aspects of empathy in psychotherapists (Hassenstab et al., 2007). When compared to control subjects, psychotherapists showed higher empathy scores when making inferences based on language mirroring cognitive aspects. Affective aspects of empathy did not differ between both groups though psychotherapists showed better emotion regulation with less personal distress in response to the distress of others. Though preliminary because of the low number of cases ($n = 19$), this psychological study supports the crucial importance of empathy in psychotherapists. Certainly though further studies are necessary to reveal the exact role of empathy and its distinct aspects (sensory, cognitive, affective; see also Zanocco et al., 2006) in psychotherapeutic interaction. Furthermore, one may investigate whether the neural network implicated in empathy (insula, anterior cingulate, thalamus, temporoparietal junction, amygdala; see Frewen et al., 2008) may show a higher neuronal reactivity in psychotherapists when compared to non-psychotherapists. Ideally, one would include neuronal and psychophysiological (skin conductance, heart rate, etc., see Marci and Riess, 2005) measures of the psychotherapist's emphatic abilities as confounding variables, i.e., as regressor or co-variate, in the measurement and analyses of the client's neuronal changes during psychodynamic psychotherapy.

Why consider the personality and empathic abilities of the psychotherapist as a confounding variable? Imagine, for instance, a psychotherapist with strong tendencies to identify with the patient. This, of course, enables the therapist to understand the patient and also, a client who has great difficulty internalizing significant others might well benefit from such an empathic psychotherapist and a supportive approach. On the other hand, however, it might hinder his empathic abilities and may also be problematic when he encounters for instance a depressed client who has internalized highly ambivalent object relationships. This case might be problematic for therapeutic interaction (e.g., when the transference is directed by these ambivalent aspects of the patient's internalized relationships). Sandler et al. (2011) also points out that for a successful psychotherapy beyond the actual transference relationship, which enables the transference neurosis; a different form of relationship—a "working alliance"—is required. This should also enable the patient to maintain an analytic attitude even if the transference conflicts are intense. Psychotherapeutic effects might thus not only depend on the

**Table 1 | Input, empirical variables, and experimental measures.**

| Input | Empirical variables | Experimental measures |
|---|---|---|
| Psychotherapist | Personality, empathy | Scales for personality and empathy |
| | Psychotherapeutic intervention as input | Psychotherapeutic identity |
| | Psychotherapeutic output | Psychodynamic, subjective, and behavioral measures |
| | Psychodynamic process mediating between psycho-therapeutic input and output | Measurement of psychodynamic process with STIPO, OPD, etc. |
| | Attachment style | Adult Attachment Interview (AAI), Adult Attachment Prototype Rating (AAPR), etc. |
| Client/Patient | Personality and psychodynamic structure as input | Measurement of psychodynamic process with STIPO, OPD, etc. |
| | Behavioral and subjective input in the gestalt of symptoms | Likert scales, reaction times, and other behavioral parameters |
| | Therapeutically-induced changes in subjective and behavioral output | Psychophysiological measures like skin conductance, etc. |
| | Attachment style | Adult Attachment Interview (AAI), Adult Attachment Prototype Rating (AAPR), etc. |
| Patient-psychotherapist-match | Quality of therapeutic relationship | Scales for measurement of fit of match between client and therapist and thus of therapeutic relationship with Helping Alliance Questionnaire (HAQ), Vanderbilt Psychotherapy Process Scale, Working Alliance Inventory |
| Investigator | Concept and hypothesis of brain function | Localization vs. integration |
| | Behavioral task as activation paradigm and input | Neurophysiological, methodolo-gical, psychodynamic, symptom-matic, and experiential demands |
| | Changes in neuronal activity as output | Method of measurement (fMRI, PET, etc.) |

personality and psychic structures of the psychotherapist himself but also on the specific constellation between therapist and client including their respective attachment styles (see for instance Schauenburg et al., 2006). This makes it clear that experimentally we do not only need to include personality scales for both the client and the therapist but measures for attachment styles on both sides, e.g., the Adult Attachment Interview (AAI; Hesse, 1999) or the Adult Attachment Prototype Rating (AAPR; Straußet al., 1999).

Another variable the psychotherapist himself puts in are of course the psychotherapeutic interventions he uses to induce psychotherapeutic change; the factor accounting for the psychotherapeutic intervention may be conceptualized as "psychotherapeutic input" which describes the intervention the psychotherapist uses to induce therapeutic change in the client. Freud (1937) tackles the desired changes in psychotherapy and appropriate therapeutic interventions, when he raises the question of the "natural end of the analysis." He emphasizes that therapeutic interventions should be aimed at overcoming the patient's inner resistances, and thus the symptoms he is suffering from will disappear. It is a question of undoing "ego-changes," which are created by mobilizing ego-defenses against dangerously experienced drive-derivative in the course of development. This makes up the analytical process. The therapist may, for instance, maintain a state of analytic abstinence together with an evenly suspended attention as a basis for interpreting unconscious conflicts, the transference or dreams. Or he may choose to focus on working with imagination letting the client imagine various kinds of scenarios to put traumatic events into a broader context. Contrary to long-term psychoanalytical psychotherapy, the therapist may focus—within the framework of short-term psychodynamic psychotherapy—on so-called core conflictual relationship themes (CCRT) or interpersonal conflicts in the actual relationship of the patient (Luborsky et al., 1985; Luborsky and Crits-Christoph, 1989; Roth and Fonagy, 1996). This must be accounted for in a quantified and objective way as for instance by the recently developed questionnaire of psychotherapeutic identity that asks for various issues of the psychotherapists' education, experience, style, and values (see Klug et al., 2004).

In addition to psychotherapeutic input and psychodynamic process, we also need to account for the psychotherapeutic output, the effects. There have been various studies showing the therapeutic efficacy of psychodynamic psychotherapy (see for instance Leichsenring and Leibing, 2007; Haase et al., 2008; Leichsenring and Rabung, 2008; Taylor, 2008). Recently developed instruments like the Operationalized Psychodynamic

Diagnosis (OPD-2; Cierpka et al., 2007; Boeker and Richter, 2008; Boeker et al., 2008; OPD-Task Force, 2008) enable an operationalized psychodynamic diagnostic approach based on a multiaxial system (consisting of four psychodynamic axes and one descriptive axis). Furthermore, OPD enables the definition of relevant therapeutic foci and the measurement of therapeutic changes (Rudolf et al., 2004). The Structured Interview for Personality Organization (STIPO; Clarkin et al., 2004) was developed according to the psychodynamic concept of Kernberg (1996). The STIPO allows the evaluation of an individual's personality organization with respect to the following dimensions: identity consolidation, quality of object relations, use of primitive defenses, quality of aggression, adaptive coping vs. character rigidity, and moral values. The psychotherapeutic output is accounted here only on a psychodynamic level; this is problematic because the measure that measures something, the psychotherapeutic output, should be different from what it shall measure, the independent variable in the experimental design (which though remains constitutively dependent on it). Therefore, what is needed additionally are some dependent variables of psychotherapeutic change and their underlying psychodynamic processes on a different level, the subjective and behavioral level.

One might argue that the neural effects themselves may well-serve as dependent though different measure of psychotherapeutic outcome. This however is to confuse different evidences. The neural effects are supposed to evidence the effects of psychotherapy on the neural level while they are not supposed to reflect evidence of the psychotherapeutic effects by themselves. We cannot measure and evidence psychotherapeutic effects by neural measures, that are supposed to mediate them if we want to avoid circularity. Hence, to reliably link neural effects to psychotherapeutic effects, we need a measure of psychotherapeutic effects that is neither psychodynamic, thereby avoiding identity with the output, nor neural in order to avoid identity with the process that is supposed to mediate its effects. As such a measure Beutel (2009) suggests changes in the known memory systems—declarative (explicit) and procedural (implicit)—, that (memory) in turn can be localized in specific brain structures. He discussed that the repression which has been overcome by analytic interventions, can lead to the repressed being recalled and then being reproduced and detected by memory tests. The findings of Nader et al. (2000) confirm the well-known fact in memory research that memory performance is affected by the constellations of encoding and retrieval situations and may distort the memory of content ("false memory," Loftus and Ketcham, 1994). In contrast to these findings, we assume that the influence of the memory is insignificant in the constellation of the encoding and the retrieval situation, because it retrieves meaningful biographical information. Thus, memory systems can on the one hand reflect the effects of psychotherapy; on the other hand they can be localized in specific areas of the brain itself. However, this requires a careful conceptualization of such experiments: first, the confounding variables should be detected (e.g., influencing memory performance by the current emotional state of the patient/subject) and controlled, and secondly a careful selection of test instruments should be made. Only then can the memory performance be a measure that maps evidence of the effects of psychotherapy on the one hand, and locates and maps the neural level on the other hand.

### *The client as "input"*

First and foremost, the client comes with a specific psychodynamic constellation and his particular personality, his psychodynamic and personality input. For instance, a certain mechanism may predominate to such a degree that it becomes pathological [e.g., introjection in the "introjective type" of depressed patients (see Blatt, 1974; Boeker et al., 2000; Taylor and Richardson, 2005)]. Consequently, more mature mechanisms cannot be used. The psychodynamic constellation of the client needs to be objectified and verified and several instruments like the OPD-2, the STIPO, and the KAPP (Weinryb et al., 1991a,b) have been developed for this purpose. These three are rating instruments based on psychoanalytical theory to assess relatively stable modes of mental functioning as they appear in self-perception of the own personality and interpersonal relations. In addition, one should also include measures of the personality like the Temperament Character Inventory (TCI) that measures various dimensions of reward (reward dependence, novelty seeking, etc.) and self (self-directedness, self-transcendence, etc.).

One possible confounding factor in experimental neuro-imaging studies of patients in psychodynamic psychotherapy could be a potentially conflicting situation of the "patients" being at the same time the "subjects" in the neuro-imaging study, as their willingness to participate in the study can be seen under the point of view of their transference situation.

However, the client does not come to the psychotherapist because of his specific psychodynamic constellation. He comes because he encounters some behavioral and subjective problems which outside observers may call symptoms. These symptoms are the aim and targets of the psychotherapeutic intervention. For instance, a client with high degree of introjection does not come because of his abnormally high introjection but because he may be severely depressed and it is his depressive symptoms that are the target of psychotherapeutic intervention. What we need to account for experimentally is thus the behavioral and subjective problems encountered by the client, i.e., his symptoms. They may for instance be measured subjectively with scales like the Beck Depression Inventory (BDI; Beck et al., 1996) or the Beck Hopelessness Scale (BHS) where the client himself rates and evaluates his subjective and behavioral problems. Or the client's problems may be rated objectively by somebody else using for instance the Hamilton Depression Rating scale (HDRS). In order to avoid confusion between psychotherapeutic intervention and symptom measurement, objective scales shall be accounted by a person that is different and independent of the psychotherapist himself since otherwise some bias and contamination by the latter cannot be excluded. Most importantly, what is needed here in the future is a clear empirical linkage between specific psychodynamic processes and particular symptoms, i.e., behavioral and subjective abnormalities. For instance, introjection or anaclitic needs have often been associated with depression (see Blatt, 1974). Referring to the psychotherapeutic context of introjection, Blatt's distinction between introjective and anaclitic depression is of special

importance. Patients suffering from anaclitic depression are primarily preoccupied with issues of interpersonal relatedness (e.g., trust, caring, intimacy, and sexuality) and use primarily avoidant defenses (e.g., denial and repression) to cope with psychological conflict and stress. In contrast, patients suffering from introjective depression are primarily concerned with establishing and maintaining a viable sense of self, ranging from a basic sense of despair, to concerns about autonomy and control, to issues of self-worth, and use primarily counteractive defenses (e.g., projection, doing and undoing, intellectualization, reaction formation, and over-compensation). Interestingly, this differentiation is significantly related to different kinds of outcome in long-term intensive treatment of seriously disturbed young adults, and different responses to two forms of therapy—psychoanalysis and psychotherapy (cf. Blatt, 1993). What is needed are studies to show the correlation between both psychodynamic and symptomatic measures entailing what we call psychodynamic-symptomatic specificity.

Finally, we need to account for the change in the client as induced by the psychotherapy. These changes may be measured in behavioral and psychodynamic terms as discussed above and should also be accounted for in subjective terms. For instance, one hypothesis is that introjection may be accounted for by what we call self-related processing (Boeker and Richter, 2008; Northoff, 2008). If so one would expect increased self-relatedness in depressed patients when compared to healthy subjects which is indeed the case as demonstrated recently (Northoff, 2007; Grimm et al., 2009). Psychodynamic psychotherapy should lead to a decrease in the self-focus in depressed patients which ideally should be accompanied by decreased introjection. If so, the subjective experience of self-relatedness may be taken as a marker of subjective change induced by psychodynamic psychotherapy. This may be accompanied ideally by behavioral markers like reaction time measures during tasks implicating self-relatedness. Most importantly, the subjective and behavioral measure of self-relatedness should be sensitive to both, the psychodynamic processes as induced by psychotherapeutic intervention, and the symptoms, i.e., the clients' behavioral and subjective input. This means that self-relatedness should serve as dependent variable of both introjection and depressed symptoms and that the latter two should also be linked in functional regard. All three, self-relatedness, introjection, and depressed symptoms are thus closely linked to each other in functional and hence constitutional regard while experimentally they should be kept distinct and separate. We are thus again confronted with the discrepancy between clinical and experimental levels encountering the constitution of clinical symptoms by various interdependent functions which though experimentally need to be kept apart and thus independent of each other.

### *The therapeutic relationship as input*

Over the past decades the psychoanalytical situation was reconceptualized as a dyadic system in which the psychoanalytic psychotherapist is both participant and observer. The broadened definition of counter-transference and the influence of object relations theory and various intersubjective perspectives have led to increased emphasis on the relationship between psychotherapist and patient. Many new terms have been coined to emphasize various facets of the "two-personness" of analysis including the therapeutic alliance and the "real" relationship (cf. Vaughan and Roose, 2000). The most far-reaching attempt to distinguish transference-countertransference from "reality" aspects of the dyad has occurred in the context of the growing emphasis on patient-therapist match.

Kantrowitz et al. (1989) defined match in the following way: match is "a broader field of phenomena in which counter-transference is included as one of many types of match. The individual history, characteristics, attitudes, and values of each analyst and patient predispose them respectively to certain counter-transference and transference reactions. Match, however, can also refer to observable styles, attitudes, and personal characteristics which are rooted in residual and unanalyzed conflicts, shared or triggered in any patient-analyst pair" (Kantrowitz et al., 1989, p. 895). Different types of facilitating and impeding matches are distinguished from one another which based on similarity and complementarity very much resemble the concordant and complementary transference-countertransference paradigms delineated by Racker (1968) within an object relations model. The importance of interactive, non-verbal affective communication that shapes the behavior and response of the patient and the therapist also needs to be pointed out as one central factor constituting the match (cf. Kantrowitz, 1995).

Some psychotherapy studies have focused on the question of what constitutes a good match. Luborsky et al. (1988) observed that from ten pre-treatment demographic variables (age, marital status, having children, religion and level of religious activity, education, cognitive style, etc.) only match in marital status was found to be significantly predictive of positive outcome (see Garfield and Bergin, 1978; Gruenbaum, 1983; Hollander-Goldfein et al., 1989, for other studies in this direction).

Recently, instruments to measure the fit or match between therapist and client have been developed. The Helping Alliance Questionnaire (Luborsky, 1984) investigates the subjective evaluation of the therapeutic relationship from the perspective of both the client and the therapist so that the correlation between both may reflect the fit or "match." Another instrument is the Vanderbilt Psychotherapy Process Scale (O'Malley et al., 1983) that allows an evaluation of the client-therapist relationship by means of an external observer as for instance a video recording. It includes dimensions like patient involvement, therapist-offered relationship and exploratory process. Finally, the Working Alliance Inventory (Horvath and Greenberg, 1989; see also Bordin, 1975, 1976) includes 36 items to the dimensions goal, task and bond that can be evaluated by the client, the therapist, and an external observer.

Taken together, there is still a need for psychotherapeutic research that collects data from both participants in dyadic situations. To date there are only very few studies attempting to operationalize different factors of the therapeutic relationship and developing adequate paradigms using neuro-imaging approaches (see Kaechele and Buchheim, 2008).

### *The investigator as input*

The investigator targets the brain; more specifically he aims to reveal the neural effects of psychodynamic psychotherapy. By developing his hypothesis about possible neural effects, he must presuppose (either implicitly or explicitly) a specific concept and theory of brain function. For instance, presupposing strict localizationism and modularity, he may hypothesize that neural activity in a specific region like the often observed abnormality in the subgenual anterior cingulate cortex (Mayberg, 2003) may be changed and normalized by psychodynamic psychotherapeutic intervention in depression. This hypothesis is based upon similar observations in CBT and pharmacotherapy (see Goldapple et al., 2004; Kennedy et al., 2007). However, these and almost any other brain imaging study on the neural effects of psychotherapy do show a wide variety of different regions showing neural changes. This puts the presupposition of strict localization into doubt and may make a different concept and theory of brain function.

Alternatively to localizationism, one may assume neuronal integration. Neuronal integration describes the coordination and adjustment of neuronal activity across multiple brain regions. The interaction between distant and remote brain areas is considered necessary for a complex function to occur, such as emotion or cognition (Price and Friston, 2002; Friston, 2003). Neuronal integration focusing on the interaction between two or more brain regions must be distinguished from neuronal segregation (Price and Friston, 2002; Friston, 2003). Here a particular cognitive or emotional function or processing capacity is ascribed to neural activity in a single area that is both necessary and sufficient; one can subsequently speak of neuronal specialization and localization. We assume that for instance mechanisms as complex emotional-cognitive interactions cannot be localized in specialized or segregated brain regions. Instead, we consider specific psychodynamic mechanisms to require interaction between different brain regions and thus neuronal integration

For neuronal integration to be possible, distant and remote brain regions have to be linked together which is provided by connectivity. Connectivity describes the relation between neural activity in different brain areas. There is anatomical connectivity for which we will use the term connections in order to clearly distinguish it from functional connectivity. In addition, Friston and Price (2001) distinguish between functional and effective connectivity: functional connectivity describes the "correlation between remote neurophysiological events" which might be due to either direct interaction between the events or other factors mediating both events. A correlation can either indicate a direct influence of one brain area on another or their indirect linkage via other factors. In the first case the correlation is due to the interaction itself whereas in the second the correlation might be due to other rather indirect factors like for example stimuli based on common inputs. In contrast, effective connectivity describes the direct interaction between brain areas, it "refers explicitly to the (direct) influence that one neural system exerts over another, either at a synaptic or population level" (Friston and Price, 2001). Here, effective connectivity is considered on the population level because this corresponds best to the level of different brain regions investigated here. For example, the prefrontal cortex might modulate its effective connectivity with subcortical regions thereby influencing specific functions like interoceptive processing.

Based upon connectivity, neural activity between distant and remote brain regions has to be adjusted, coordinated, and harmonized. Coordination and adjustment of neural activity might not be arbitrarily but guided by certain principles of neuronal integration (Northoff et al., 2004). These principles describe functional mechanisms according to which the neural activity between remote and distant brain regions is organized and coordinated. Such principles of neuronal integration might for instance include reciprocal modulation, modulation by functional unity, top-down modulation, and modulation by reversal (see Boeker et al., 2006; Northoff, 2008, for details). As hypothesized by us, each of these principles may be associated with a specific psychodynamic mechanism.

One may want to argue that the debate about the presupposed theory and concept of brain function is of mere theoretical interest while remaining empirically irrelevant. This however is to neglect that the experimental measure of neural change strongly depend upon the concepts we as investigator put into the investigation itself. If we, for instance, hypothesize a single or specific regions to be effected by psychodynamic psychotherapy, we only measure and analyze our data with regard to such localizationism. While we neither measure nor analyze brain function in orientation on for instance the above mentioned principles of neuronal integration that require different methods of analysis. This may be necessary in depression where the specific abnormality may not consist in one particular region but an abnormal reciprocal modulation between medial and lateral prefrontal cortex with both regions no longer activating in a converse, i.e., opposite and reciprocal way (see Northoff et al., 2004; Boeker et al., 2006; Grimm et al., 2006). Hence, by concentrating on changes in single regions, we may miss neural changes that are induced by psychotherapeutic effects like the normalization of for instance reciprocal modulation between medial and lateral prefrontal cortex. This demonstrates that the very concept of brain the investigator himself most often implicitly presupposes may strongly impact what and how he measures brain function and which neuronal variables can and will be linked to psychotherapeutic change.

Another crucial input by the investigator is the behavioral task he employs in brain imaging to induce changes in neuronal activity. Brain imaging may be performed in resting state and or during an activation state with the latter requiring a specific behavioral task. The choice and selection of this behavioral task is of vital importance. Functionally, the behavioral task should be linked to the psychodynamic processes targeted by the psychotherapist in psychodynamic psychotherapy as well as to the client's symptoms, his subjective and behavioral complaints. Psychotherapeutic intervention may then be assumed to contribute to "normalize" abnormal reciprocal modulation in depression. This implies for the experimental designs that the behavioral task used in scanning should recruit those neural processes and mechanisms that supposedly mediate both the psychodynamic interventions and the client's symptoms. In addition to such psychodynamic and symptomatic requirements, the behavioral task needs to meet experimental demands. Such experimental demands include careful control conditions, behavioral

and subjective measurement of the effects of the task itself, empirical linkage to the targeted neural processes and mechanisms, etc. The main problem here is to reconcile psychodynamic and symptomatic requirements with experimental demands. The unit of interest on both the psychodynamic and symptomatic level includes usually a mixture of several psychological, subjective, and behavioral variables which though on the experimental level need to be carefully controlled and spaced apart. Since the development of the behavioral task, the activation paradigm, is vital, we will discuss this issue in more detail in the next section.

## TRANSLATION PROBLEM

The above description of the design problem in its various facets reveals that different levels of investigation are involved. The translation problem deals with the methods and strategy how we can bridge the gap between the different levels. To simplify things, we want to discuss in the following four examples with each showing one pair of different levels. We will contrast personal and neuronal levels, psychodynamic and processual levels, and first- vs. third-person levels (see **Figure 2**).

### *Personal and neuronal levels: persons vs. brains*

The psychotherapist and the client are individual subjects and must therefore be characterized as persons. The brain, in contrast, is not a person but rather an object. Though this seems obvious it has major implications in both conceptual and empirical regard. Let us consider first the conceptual implications. Bennett and Hacker (2003) warn not to confuse individual subjects with their brains because that means to neglect the basic difference between persons and objects; they speak of what they call mereological fallacy where the whole, i.e., the person, is confused with one of its parts, the brain. This means for instance that one cannot say that the brain thinks, feels, or acts since these attributes belong only to persons.

What is treated in psychodynamic psychotherapy is not the brain but the person. We may treat the person in a neurophysiologically-constrained way by considering neural processes and mechanisms in our psychotherapeutic interventions but this concerns only the neural processes that supposedly mediate the therapeutic outcome. Thus, to argue that we treat the client's brain rather than himself as person is not only to confuse person and brain but also to neglect the difference between neural processes/mechanisms and psychotherapeutic output. Neural processes and mechanisms concern the brain and may be regarded a necessary though not sufficient condition of psychotherapeutic output since other factors like interpersonal constellations, the cultural environment etc., have to be considered too.

The psychotherapeutic output, in contrast, concerns the level of the person that of course is somehow related to the brain but should at least conceptually not be identified with it. Hence, psychodynamic psychotherapy targets the person rather than the brain though its effects may, at least in part, be mediated neurally and thus by the brain. This implies that we should not aim to map the psychodynamic concepts in a one-to-one way with neural activity in particular brain regions or networks and thus to strive for what is described by the concept of "neural correlates." This is so because that would mean to neglect the various other factors or variables that are implied and included in psychodynamic concepts as we saw in the specific case of psychotherapeutic intervention. Instead of the concept of neural correlates one may therefore want to preferably use the concept of "neural mechanisms" that, unlike the concept of neural correlates, does not presuppose one-to-one mapping between psychodynamic concepts and neural activity. As such neural mechanisms are supposed to underlie (rather than correlate with) psychodynamic concepts and thus psychotherapeutic interventions which leaves open conceptual and empirical space for including variables other than purely neural ones.

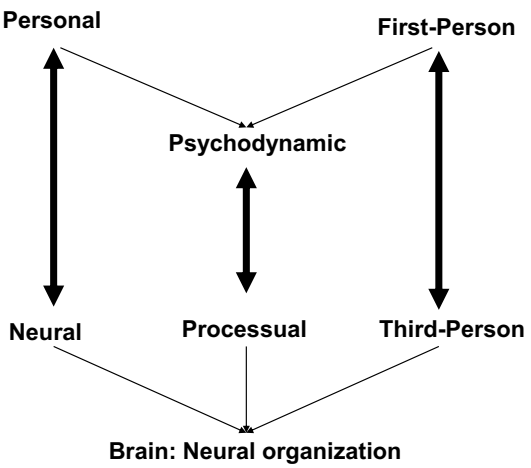


**FIGURE 2 | Different levels and the translation problem.**

### *Personal and neuronal levels: generality vs. individuality*

Another important empirical implication of the conceptual difference between persons and objects is the difference between individual and general levels. Persons concern individual subjects each with major idiosyncrasies both psychodynamically and neurally. The focus of psychodynamic psychotherapy is always on the individual, its specific subjective and personal contents as derived from its life history. Psychoanalysis gives us a conceptual framework to link these individual contents, as they are experienced from the inside of the experiencing person itself, to general structures of the psyche of persons, as they are observed from the outside by the observer. Neuroscience, in contrasts, concerns the brain as we can observe it from the outside; thereby however the individual person's specifics get lost because the experimental approach averages across different individual subjects. The difference between individuality and generality marks a principal difference between psychoanalysis and neuroscience which is nicely expressed by David Milrod (2002, pp. 22–23) in the following quote: "Neuroscientists strive to explain fundamental phenomena such as perception, consciousness, emotion, memory, etc., including the subtleties of their integration, and in this way build up an understanding of the basic functioning of the organism. In recent years they have included a study of the self as it integrates with consciousness, emotion, and awareness of

the object . . . In short, they concern themselves with the universal and objective. Psychoanalysis, which has historically focused on the individual and has been more interested in ontology, has as its goal the understanding of protracted intrapsychic, interpersonal, and subjective functioning of the individual. It was in order to better understand that functioning that psychoanalysts had to deal with the self and its representation. In dealing with the self, the psychoanalyst is more likely to focus on the contents of the self and its representation, the state of stability or fragility it may possess . . . In other words, they focus on those elements that make each individual different from one another."

How can we bridge the principal difference between the individual level of persons and the general level of brains? One way is to investigate only single cases and to focus on case studies (see for instance Solms and Lechevalier (2002) with regard to lesions patients as well as Overbeck et al., 2004; Rudolf et al., 2004; Lai et al., 2007; Lehto et al., 2008, for single case studies of psychodynamic psychotherapy and brain imaging). This however precludes a deeper insight into the neural processes and mechanisms that may eventually mediate psychotherapeutic output. What we need to develop are experimental designs and analyses that allow to take the individualized data as starting point and then to take and preserve these individual features as starting point for group analyses without averaging and generalizing them out into a group mean.

One may for instance imagine that the regions of interest in the individual subjects are taken as starting point for averaging and group analysis. The individual regions of interest may not only be determined and oriented on anatomical constraints but also psychodynamic constraints like the predominance of a certain psychodynamic mechanism. Another possibility is to group the individual subjects according to their subjective or psychodynamic profiles as revealed in empirical investigation of subjective experience. For instance, subjects with "high scores of introjection" may then be grouped together and compared with those showing "low scores of introjection." One of the major methodological challenges in the future is thus to develop experimental designs and ways of analyses that allow to link individual and general features on the neural level in the same way Freud achieved it on the psychological level in such an ingenious way.

#### *Personal and neuronal levels: content vs. organization*

Another issue in this regard is the difference between neural contents and neural organization. Psychodynamic concepts may mirror the general organization of psychological activity which then may be manifest and realized in specific psychological contents of that individual person. This parallels to the neural level. We mentioned above that one may search for principles of neural integration rather than specific regions and networks. Specific regions and networks mirror what may be called neural contents and these are the targets in for instance the search for the neural correlates of consciousness (NCC) presupposing mere correlation and one-to-one mapping strategies. The principles of neural integration refer rather to the organization of neural activity and hence to what we call neural organization.

If one now searches for psychodynamic concepts in specific neural regions and networks, one may attempt to link structures of psychological organization with neural contents. This however may be doomed to fail because one then confuses the level of organization, as presupposed on the psychological level, with the level of contents, as implied by the neural level, with both remaining unable to match or correspond on a one-to-one basis. Instead, one may rather link psychodynamic concepts to the neural organization with both presupposing and implying analogous structures. This however remains rather speculative at this point (see Northoff, 2011, for a first attempt in this sense with regard to the self) since especially the principles and structures of neural organization, as distinguished from neural contents, remain to be explored.

#### *Psychodynamic level vs. process level*

One of the main issues is the translation of psychodynamic concepts into processes that then can be psychologically and neurally investigated. Consider again the example of introjection as a psychodynamic mechanism.

Introjection is considered a psychodynamic mechanism that, based on Mentzos (1995), can generally be determined as a form of appropriating and relating objects to the subjects in a personal way that is called internalization. Internalization includes three different mechanisms, identification, introjection and incorporation. These mechanisms of identification depend on different structural levels of the ego functions and of the personality. Incorporation describes that the subjects incorporates and integrates objects into itself so that the object becomes part of the subject itself with the former being indistinguishable from the latter. The subject may also introject the object.

What distinguishes introjection from identification and incorporation (cf. Meissner, 1978)? The separate reality of the object is acknowledged by the subject in introjection but the object relations are highly ambivalent including aggressive and narcissistic conflicts and feelings of anxiety, which are defended by projective mechanisms. In contrast, identifications depend on differentiated, continuous object relations and enable a selective internalization of partial aspects of the object. Ambivalent emotions may be tolerated and expressed. Incorporations, introjections, and identifications are important steps and components of the maturation process. Disturbances of the maturation process may lead—in a psychological developmental and psychoanalytical perspective—to the development of pathological defense mechanisms and the reactivation of early modes of internalization and object relationships (e.g., introjection in depression and Borderline, see Boeker et al., 2006).

Introjection allows the distinction between subject and object by the subject; however the price for acknowledging their difference consists in ambivalence with subsequent affects and anxieties. Metaphorically speaking, the object becomes strongly affectively colored by the subject while at the same time retaining its separate reality and reality for the subject. By means of affective involvement, the object is thus subjectified and related to the subject or, as one could say with Mentzos (1995), something objective(-object) is transformed into something subjective(-object): the parenthesis are included because the object becomes only colored by subjectivity while retaining its status as object whereas in projection, as the opposite of introjection, one would

probably speak of objective-subject. The result of this process of introjection may be what is called an introject, the internal representation of an object. An object can be internalized and introjected and thus become an introject only if it has a special meaning and personal significance to the subject which usually is reflected in strong emotional involvement with the respective emotional feelings. If, for, instance, somebody has a rather close but ambivalent and therefore a strongly emotionally loaded relationship to her/his mother, the mother as object may become internalized and introjected to resolve the ambiguity in the relationship resulting in the mother being an introject for the subject. If, in contrast, the relationship to the mother is positive and free of ambiguity, it is possible to identify with the mother selectively as well as being separated from her.

This short description of introjection points out some cardinal psychological processes like relating objects to the person's self which has recently been described as self-related processing (Northoff et al., 2006). Moreover, it is clear that emotion processing is involved and closely linked to self-relatedness. Furthermore, the ability to relate to other people that involves empathy is crucial in introjection. At the same time however self-awareness is also involved since otherwise the introjecting person remains unable to distinguish itself as subject from the object, i.e., from other persons. These psychological processes that then could be regarded as starting point for developing a neuro-psychodynamic hypothesis of introjection. Accordingly, a translation from the level of a psychodynamic concept, i.e., introjection, to a process level, i.e., self-related and emotional processing etc., is needed to develop neuro-psychodynamic hypotheses and appropriate experimental designs. The psychological processes that may eventually be involved in psychodynamic concepts may then be used as guiding thread for where to look in the brain and what kind of principles of neural organization may be involved.

#### *First-person level vs. third-person level*

Systematic examination and evaluation of subjective experience must preserve its richness and complexity on the one hand, and objectively quantify its main characteristics on the other. Objectification and quantification of subjective first-person data allows for scientific investigation and consequently for establishing what can be called a "science of experience" (Gabbard, 2000). Based on a "science of experience," a "science of psychodynamic processes" needs to be developed. The "science of psychodynamic processes" should place great emphasis on patients' mental life or inner experience in order to preserve the richness and complexity of subjective experience and clinical description. At the same time, these subjective features must be objectified to provide reliable and quantifiable data. This can be achieved by asking the subjects to complete rating scales. For example, visual analog scales (Weinryb et al., 1991a,b) with regard to personal identity or idiographic instruments like the Repertory Grid Test (Boeker et al., 2000) which enables the evaluation of idiosyncratic experiences and views by means of a semi-quantitative measurement, might be applied to let the subjects themselves evaluate their experiences. One might also apply structured interviews with valid and reliable instruments for evaluation of the subjects' relevant psychodynamic features by an experienced investigator. General instruments include, for example, the Karolinska scale that assesses different psychodynamically-relevant dimensions of a person's structure (Weinryb et al., 1991a,b). Another instrument is the Operationalized Pychodynamic Diagnosis (OPD-2; OPD-Task Force, 2008) which examines three psychodynamically relevant axes interpersonal relations, conflict and psychic structure, an axis on the experience of the illness and prerequisites for treatment and one descriptive axis (psychic and psychosomatic disturbances according to ICD-10 and DSM-IV).

One of the main methodological challenges in investigating the neuronal processes underlying mechanisms is to link these first-person data about psychodynamic processes to third-person observation of neural states. Being based upon subjective experience, psychoanalysis relies on first-person data or more precisely on data obtained by introspection that presupposed what may be called Second-Person Perspective (which in the following we will subsume under the concept of First-Person Perspective). This contrasts with neuroscience which requires third-person observation of neuronal states. Due to the neglect of first-person subjective experience, neuronal states as third-person data can be quantified and objectified. This, in contrast, remains impossible in the case of first-person data which are rather qualitative and subjective. If, however, the neuronal processes of mechanisms are to be investigated, subjective experience and neuronal states (i.e., first- and third-person data) have to be linked to each other in a systematic way. For this purpose, we have created an appropriate methodological strategy, First-Person Neuroscience, which aims at systematically linking first- and third-person data (see Northoff, 2007) that also conceptualizes many investigations in current brain imaging that correlate subjective experiential variables (as for instance in visual analogs scales) with neural measures of brain function (see for instance Grimm et al., 2009).

We define "First-Person Neuroscience" as a methodological strategy to systematically link first-person subjective experience to third-person observation of neuronal states. The development of such methods distinguishes First-Person Neuroscience from neuroscience as it is commonly practiced which most often relies on third-person observation of neuronal states more or less independently of subjective experience. The main challenge in establishing First-Person Neuroscience consists in linking the individual contents of subjective experience to neuronal states. How can we link subjective experience to neuronal states?

Linkage between subjective experience and neuronal states requires two steps: first, subjective experience needs to be evaluated systematically including objectification and quantification of subjective data. Such "science of experience" is a necessary precondition for any linkage between subjective experience and neuronal states. Second, the systematically objectified and quantified subjective data then enable the linkage to analogous data about neuronal states. For this, special methodological strategies need to be developed—this is the core of what we call "First-Person Neuroscience." The above described discussion of how to translate the psychodynamic concept of introjection, that experimentally is accounted for by first-person data, into a behavioral task as activation paradigm, that yields third-person data about the brain, can be regarded as example of how to link first- and

third-person perspectives and may therefore be regarded an instance of First-Person Neuroscience.

## INDIVIDUALIZED PARADIGMS IN NEURO-IMAGING: STATE OF THE ART

### EXISTING APPROACHES

Over the past years, a number of studies have employed neuro-imaging methods in psychoanalytically oriented research. The importance of individualized experiments in studying psychotherapeutic changes, for instance, has been stressed by Kessler et al. (2011b, 2012). Though neurobiological changes in some (single) cases undergoing psychodynamic psychotherapy have been reported, mostly using Single-photon Emission Computed Tomography (SPECT) (Viinamäki et al., 1998; Saarinen et al., 2005; Lai et al., 2007; Lehto et al., 2008) with few using functional Magnetic Resonance Imaging (fMRI) in studies of obsessive compulsive disorder, panic disorder, and somatoform disorder (Overbeck et al., 2004; Beutel et al., 2010; deGreck et al., 2011). To date, studies examining the functional neuroanatomy of psychotherapy in depressed patients involved IPT or CBT (Roffman et al., 2005; Linden, 2006). Buchheim et al. (2012) were the first to conduct an fMRI study with depressed patients treated with psychodynamic psychotherapy using two fMRI paradigms (Kessler et al., 2011a, 2012; Taubner et al., 2012). The first paradigm was based on clinical material drawn from OPD-2 interviews. Kessler et al. (2011a, 2012) confronted patients with themes of their maladaptive interpersonal relationship patterns, presenting them sentences in the scanner which were derived from an OPD interview. They individually selected four sentences for each person representing a core dysfunctional relationship theme. During the control condition (traffic) patients recalled a stressful traffic situation they had experienced inducing negative emotions and recalling autobiographical memories. Conditions were separated by a "relaxation" condition. The second paradigm, described by Taubner et al. (2012), used attachment-related pictures from the Adult Attachment Projective Picture System (AAP). They aimed at eliciting mental engagement with attachment-related experiences such as loss, illness, danger, and separation. During an AAP interview patients described the scene in the picture including what characters were thinking and what could happen next. From this interview three sentences representing the attachment pattern of each patient were extracted. As control condition participants were shown the AAP pictures and were invited to only describe the environment depicted.

Methodological shortcomings in these fMRI paradigms can be discussed such as the elevated cognitive demand implied by a reading task, unsatisfying control conditions and difficulty concerning the selection of stimuli. These methodological concerns are expression of the complex endeavor that the investigation of neural mechanisms of subjective experience implies (Logothetis, 2008). Developing valid experimental designs taking into account the very individual dimension of experience is an arduous methodological challenge, as it has been illustrated here before. In the following section, our attempt to create a new experimental design for the investigation of neural mechanisms in depressed patients during psychodynamic psychotherapy will be depicted.

Coherent with the above-described methodological strategy named "First-Person-Neuroscience" the experimental design aims at systematically linking subjective experience to the observation of neural states. This necessitates the objective evaluation of subjective experience in a first step. In a second step, the so created data has to be linked to observations on the neural level.

To begin with, we will outline our choices of how to evaluate subjective experience, giving a brief description of the axis "interpersonal relations" from the OPD-2 (OPD-Task Force, 2008) as well as the Maladaptive Interpersonal Patterns Q-Sort (MIPQS; Zimmermann et al., accepted). We will then describe the development of the "Interpersonal Relations Picture Set" (IRPS) and a new neuro-imaging experiment based on the IRPS.

### THE OPD-2 AXIS "INTERPERSONAL RELATIONS" AND THE MALADAPTIVE INTERPERSONAL PATTERNS Q-SORT (MIPQS)

An adapted instrument to attempt an objective evaluation of subjective experience is the OPD-2 (OPD-Task Force, 2008). It operationalizes psychodynamic dimensions in different diagnostic axes. Regarding depressive disorders, the axis "interpersonal relations" is particularly relevant, as depressive disorders go along with various impairments in interpersonal and social functioning. For example, depressive patients tend to have deficits in emotional expression and emotion recognition in others. They also tend to have difficulties with affective modulation in basic interpersonal communication of emotions and feelings. Broadly speaking, psychodynamic psychotherapy sets a specific focus on these affective processes using phenomena of transference and countertransference. The axis "interpersonal relations" of the OPD-2 offers a classificatory system describing different patterns in interpersonal behavior. This diagnostic axis enables clinicians to assess and precisely describe specific maladaptive interpersonal patterns in patients with depression.

Recently, the Maladaptive Interpersonal Patterns Q-Sort (MIPQS), a self-report version of the OPD-2 axis "interpersonal relations," has been developed (Zimmermann et al., accepted). Using a card sorting procedure, the MIPQS allows the establishment of a subjective and hierarchized profile of typical interpersonal behavior. One of its substantial advantages compared to the OPD interpersonal relation axis is the facility in its use. The MIPQS exists in two versions. The MIPQS-A is a self-evaluation of the participant concerning typical interpersonal behavior. In contrast, the MIPQS-B enables the clinician to evaluate the participant's interpersonal behavioral patterns from his point of view and based on the interview situation. We will concentrate here on the MIPQS-A. The card sorting procedure of the MIPQS-A (named MIPQS in the following) comprises two steps. In a first step, the participant rates the relevance of behavioral patterns (described by 32 items) in his own behavior toward significant others. In a second step, the participant rates the relevance of described behavioral patterns (equally 32 items) in the behavior of others toward himself. The description of patterns in interpersonal behavior was adopted from rating items of the OPD interpersonal relation axis. These items are theoretically close to interpersonal circumflex models such as used in interpersonal psychology (e.g., the SASB/Structural Assessment of Social Behavior model, Benjamin et al., 2006). The SASB model

describes different qualities of interpersonal behavior by means of two orthogonal and bipolar dimensions: control (dominant vs. submissive) and affiliation (friendly vs. hostile). The MIPQS items have been empirically tested and can be located in the circumplex model comprising these two dimensions. Every one of the 32 MIPQS items consists of two easy to understand descriptions of a specific interpersonal behavior pattern like "I tend to ignore others or give them the cold shoulder" and respectively "Others tend to ignore me or give me a cold shoulder." They are printed on separate cards. The sorting procedure includes the depositing of the 32 cards on finally nine columns ranging from "most typical" to "most untypical" with "unimportant" as the fifth column. Furthermore, the instrument offers a sequential ranking of all items from 1 (most untypical) to 32 (most typical).

Based on the items of the MIPQS we have developed graphic illustrations forming the so-called "Interpersonal Relations Picture Set" (IRPS), which we plan to use in fMRI experiments. In the following the different steps of its development will be described.

## THE INTERPERSONAL RELATIONS PICTURE SET (IRPS)

The MIPQS provides 32 items describing patterns of interpersonal behavior. The IRPS comprises pictures illustrating interpersonal behavior patterns. The pictures were developed step-by-step. At first, there had been an attempt to illustrate the interpersonal situations by means of multicolored symbols. However, this approach was abandoned because of the high level of abstraction of these symbols. Consecutively, a collection of pictures illustrating the different situations by means of stick figures was composed (see **Figure 3A**). The pen-drawings were scanned for further processing in a widely used image editor (Seashore©). Each picture shows two or more black stick figures on white background. The figures vary in size, but do not show any gender specification, facial expression, clothes, or other specific characteristics. Some figures, e.g., the figure taking a neutral body position, occur repeatedly in different pictures. Different interpersonal situations are expressed only in the specific posture of figures as well as their positions toward each other.

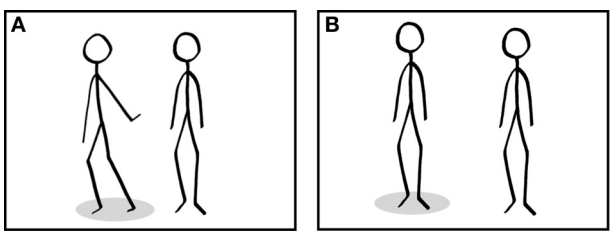


**FIGURE 3 | Example from the IRPS representing the item "I tend to ignore others or give them the cold shoulder" (A) and an example of a picture from the control condition (B) used in the fMRI-experiment.** Please note that style and number of the stick figures and the basic characteristics of the pictures are matched across conditions. Subjects are asked to take the interpersonal perspective of the figure indicated by the gray marker.

### VALIDATION OF THE PICTURES

Concerning the testing of these pictures, ethical approval, and permission was obtained for all procedures described below from the Ethics Committee at the University of Zurich. A complete and detailed description of the study was provided to participants and patients and they gave a written informed consent concerning their participation.

In order to confirm the relation of every picture to the assigned item of the MIPQS we performed an online survey. It was sent to a mailing list of the university. The survey included an introduction, an instruction concerning the questionnaire and a request of age, gender, educational level, and history of interpersonal relationships. Then the ISPS pictures were presented in randomized order. Participants were asked to judge the pictures in two conditions. Firstly, in the "discrimination task," pictures were presented combined with the matching description as well as four randomly selected descriptions out of the remaining 31 MIPQS items. Furthermore, a response that none of the offered descriptions fitted the picture was added. This form of questioning was designed as multiple choice task and only one answer was allowed. Participants were asked to distinguish the matching description from the offered choice. Secondly, in the "relevance task," participants were asked to rate the level of relevance of each picture. A nine-point Likert scale was combined with the picture and its matching description for this task. The sample of the online survey was randomly split into two groups to avoid a repetition effect. Hence, no item was presented twice in the survey. Statistical analysis was conducted using the SPSS® software package (IBM). The data for all variables collected were subjected to descriptive statistics according to the respective scale level. In order to assure direct interpretability of results of both tasks, the data analysis was limited to descriptive statistics. This included indicating the proportion of correct responses for multiple choice tasks in percentage and the median for nine-point Likert scales.

In a further step, we tested the correspondence between the IRPS and the MIPQS when participants performed them separately. A number of patients suffering from Major Depressive Disorder (MDD) were recruited from the Department for Psychiatry, Psychotherapy, and Psychosomatics of the University Hospital of Psychiatry Zurich. Patients with neurological or other physical illnesses, disorders of personality, alcohol- or substance abuse were excluded. Diagnosis was made according to DSM IV (American Psychiatric Association, 1994). Clinical symptoms were assessed with the BDI II (Beck et al., 1996) and the Hamilton Depression Scale (Hamilton, 1960). After execution of the MIPQS, patients were asked to perform the relevance task (as described above) using the experimental control software Presentation® (Neurobehavioral Systems). Ratings for each item were related to the number of the column chosen by the patient in the MIPQS using Spearman rank correlations.

### COURSE OF THE EXPERIMENT

The fMRI experiment is embedded in a large-scale psychotherapy outcome study. We investigate changes in depressed patients during 1 year of psychodynamic psychotherapy concerning psychodynamic, behavioral and neuronal parameters. Different instruments are employed for the evaluation of these changes,

such as the OPD interview, fMRI examination and a series of questionnaires: MIPQS (Maladaptive Interpersonal Patterns Q-Sort; Zimmermann et al., accepted), OPD-SF ("OPD Struktur-Fragebogen," [OPD Structure Questionnaire]; Ehrenthal et al., 2012), BDI (Beck et al., 1996), BAI (Beck Anxiety Inventory), BHI (Beck Helplessness Inventory), FKBS ("Fragebogen zu Konfliktbewältigungsstrategien," [Questionnaire on Coping with Conflicts]; Hentschel et al., 1998), IIP-D (Inventar zur Erfassung Interpersonaler Probleme [Inventory of Interpersonal Problems] Horowitz et al., 2000), HCSC ("Heidelberger Umstrukturierungsskala," [Heidelberg Structural Change Scale]). A specific focus is set on changes in interpersonal behavioral patterns such as evaluated by the MIPQS. The IRPS will be employed during the fMRI examinations. The procedure for the fMRI experiment will roughly be described here after.

In a first step, participants rate the MIPQS and the IRPS. Six pictures representing the most typical interpersonal situations for each participant are selected. Participants are then invited to develop a personal narrative for every one of the six target pictures. Ideally, this determines the individual meaning of each one of these stimuli. After, participants proceed to fMRI examinations. Instructions include a structured description of the task. Before proceeding to the fMRI examination, participants perform a trial run. Stimuli are presented in a block-design in randomized order. Four experimental conditions are used in the scanning procedure. In a first condition ("typical") the six target pictures are presented. A second condition ("untypical") consists of pictures rated beforehand by the participants as being not typically representative for their interpersonal behavior. The control condition ("neutral") includes pictures showing a number from two to four stick figures in a frontal, neutral position (see **Figure 3B**). Finally, a resting condition ("rest") showing a black fix-cross on white background is included. In order to evaluate subjective experience during the "Typical" and "Untypical" condition, a nine-point Likert scale is presented after every picture during the scanning procedure. Participants are asked to rate the level of personal involvement experienced while watching the pictures. In the "neutral" condition subjects are asked to report the number of stick figures presented in every picture. Stimuli are presented using Presentation® and all feedbacks are given using a trackball response pad (Current Designs®). The experimental design was optimized for further analysis of effective connectivity.

## DISCUSSION

We have illustrated our attempt to develop an individualized neuro-imaging paradigm. As mentioned before, the choice and selection of the behavioral task employed during fMRI examinations is of vital importance. We have chosen to base the behavioral task on a validated instrument (MIPQS) describing a central dimension in psychodynamic psychotherapy: changes in interpersonal behavior and associated feelings. We hence try to isolate a specific mechanism relevant in the psychodynamic treatment of depression and operationalize it in an fMRI experiment. The experiment incorporates a number of specific principles that are, in our view, of great importance for this type of experimental design.

First, focus is set on the very individual dimension of experience as well as their emotional implications. This is reflected in the individual choice and subjective determination of meaning of stimuli (IRPS pictures) used during neuro-imaging.

Second, the association of the picture to autobiographical experience should strengthen the affective reaction of the participant when the IRPS pictures are presented in the scanner. During the scanner procedure, participants rate their subjective emotional arousal induced by the IRSP pictures. Having a subjective rating of this kind enhances the validity of the experiment.

Third, the use of visual stimuli in form of pictures may reduce the cognitive demand on participants during fMRI examinations compared to tasks involving stimuli using words or sentences.

Fourth, the fMRI experiment comprises a valid control condition. The control condition consists in presentation of (a) IRPS pictures that the patient rated as non-relevant for himself; (b) pictures showing stick figures in a neutral position.

Results of fMRI exams will be linked to results from other diagnostic instruments such as the OPD and a series of others questionnaires. By the choice of these instruments, we tempt to take into account the complexity of subjective experience.

There are several factors that have been pointed out earlier to be relevant for the design of neuro-imaging paradigms in psychodynamic research that are not taken into account in our paradigm. This includes factors resumed under the "design problem" as well as those evoked concerning the "translational problem." For example, we have not considered the psychotherapist or the therapeutic relationship as "input" in depth. Our design includes one questionnaire possibly giving a hint on the matching of therapist and patient (IIP-D) but it does not include personality or attachment style ratings for the therapist. Ideally, this should also be taken into account. To give another example, we also need to carefully consider our hypothesis concerning neural activation during fMRI exams and take into account considerations illustrated earlier with reference to "the investigator as input."

Our experimental paradigm does not aspire to satisfy all of the requirements that experimental designs in psychodynamic psychotherapy research using neuro-imaging should ideally fulfill and which were described earlier in this article. In this vast and complex research domain, the development of adequate and valid experimental designs stays a defiant methodological challenge. Our experimental paradigm represents a further step into this direction. It aspires to create an experimental design that does reflect—even though in a limited way—the complexity of subjective experience.

## CONCLUSION

We discussed the methodological problems in designing a brain imaging study to measure neural effects of psychodynamic psychotherapy. Two main problems, the design problem and the translation problem, were encountered. The design problem points to the many inputs including the psychotherapist himself, the client, and the investigator, which each by itself may need to be included as distinct experimental variables in the study design. The translation problem refers to the different levels involved in

such project such as the personal vs. the neuronal level, the psychodynamic vs. the process level, and the First-Person level vs. the Third-Person level. Thereby the personal vs. the neuronal level is of particular interest in that it includes conceptually and empirically relevant distinctions like persons vs. brains, generality vs. individuality, and organization vs. content.

Taken together, this demonstrates that brain imaging studies of the neural effects of psychodynamic psychotherapy are confronted with a rather high degree of complexity raising various conceptual, empirical, and experimental problems. The discussion of these problems shall not discourage future investigators; instead it shall provide them with some suggestions for guidance through the jungle of complexity. Though any such investigation requires multi-professional efforts and emphatic collaboration, we are sure the merits are highly rewarding. The complexity of investigating the neural effects of psychodynamic psychotherapy mirrors in an almost paradigmatic way the complexity of our brain so that neuro-psychodynamic findings entail insight and a better understanding of the general principles of neural organization and our brain's very human nature. The answer to this question is two-fold: on one hand we do think that by revealing the neural mechanisms underlying psychotherapeutic processes, we may be able to develop more specific protocols of psychotherapy in orientation to the respective neural functions associated with the respective region. For instance, taking a rather simplistic example, if the level of neural activity in the amygdala may be involved in psychotherapeutic processes and even be predictive of psychotherapeutic outcome, it may be an additional indicator that the involvement of emotions may have been crucial in psychotherapeutic success. This may be the case even if the therapy was not emotion-focused but rather oriented in psychodynamic mechanisms. Such results may then be considered as evidence for the central involvement of emotional processes in the psychodynamic processes which may then lead to further refinement and specification of psychotherapeutic protocols. This raises not only the question for the linkage between emotions and psychodynamic processes but also how we, for example, can address emotions more explicitly in relation to defense mechanisms in psychotherapy. Such orientation on neural functions may then lead to the development of neurally-based psychodynamic psychotherapy in the future and may therefore be empirically, i.e., neurally, more plausible, and compatible with respect to the brain and its mode of function than the current purely clinically- and observationally-based approaches.

On the other hand, revealing the neural mechanisms underlying psychotherapeutic processes may also contribute in the reverse direction, by giving us a better understanding of the psychological, i.e., psychodynamic, mechanisms associated with certain patterns of neural activity across different region. Hence, it is not only that psychodynamic psychotherapy may benefit from brain imaging but also the other way in that the latter may also be complemented by the latter.

In summary, we thus assume bilateral exchange and contribution between psychodynamic psychotherapy and brain imaging. This may ultimately, as we hope, lead to the development of diagnostic and therapeutic predictive markers with especially the latter predicting what subjects may benefit from what kind of psychotherapy in general, and the kind of focus in psychodynamic psychotherapy in particular.

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# Changes in brain activity of somatoform disorder patients during emotional empathy after multimodal psychodynamic psychotherapy

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Somatoform disorder patients show a variety of emotional disturbances including impaired emotion recognition and increased empathic distress. In a previous paper, our group showed that several brain regions involved in emotional processing, such as the parahippocampal gyrus and other regions, were less activated in pre-treatment somatoform disorder patients (compared to healthy controls) during an empathy task. Since the parahippocampal gyrus is involved in emotional memory, its decreased activation might reflect the repression of emotional memories (which—according to psychoanalytical concepts—plays an important role in somatoform disorder). Psychodynamic psychotherapy aims at increasing the understanding of emotional conflicts as well as uncovering repressed emotions. We were interested, whether brain activity in the parahippocampal gyrus normalized after (inpatient) multimodal psychodynamic psychotherapy. Using fMRI, subjects were scanned while they shared the emotional states of presented facial stimuli expressing anger, disgust, joy, and a neutral expression; distorted stimuli with unrecognizable content served as control condition. 15 somatoform disorder patients were scanned twice, pre and post multimodal psychodynamic psychotherapy; in addition, 15 age-matched healthy control subjects were investigated. Effects of psychotherapy on hemodynamic responses were analyzed implementing two approaches: (1) an a priori region of interest approach and (2) a voxelwise whole brain analysis. Both analyses revealed increased hemodynamic responses in the left and right parahippocampal gyrus (and other regions) after multimodal psychotherapy in the contrast "empathy with anger"—"control." Our results are in line with psychoanalytical concepts about somatoform disorder. They suggest the parahippocampal gyrus is crucially involved in the neurobiological mechanisms which underly the emotional deficits of somatoform disorder patients.

**Keywords: psychodynamic, psychotherapy, fMRI, emotional empathy, somatoform disorder**

## INTRODUCTION

Somatoform disorders contain a group of complex diseases consisting of medically unexplained somatic symptoms (Kirmayer et al., 1994; Stein and Muller, 2008; Pedrosa Gil et al., 2009; Hiller et al., 2010).

Psychologically, they are linked to alexithymia, a construct which describes decreased emotional awareness (Sifneos, 1973; Bach and Bach, 1996; Bankier et al., 2001; Duddu et al., 2003; Grabe et al., 2004; Burba et al., 2006; Bailey and Henry, 2007; Mattila et al., 2008; Pedrosa Gil et al., 2008; Wood et al., 2009). In addition, another emotional process—emotion recognition (i.e., the correct labeling of emotions, Pedrosa Gil et al. 2009)—is impaired (Pedrosa Gil et al., 2009; de Greck et al., 2012), and somatoform disorder patients describe increased "empathic distress" (i.e., they experience themselves as being easily affected and overwhelmed by negative emotional states of others, Davis 1983; de Greck et al. 2012).

From a psychodynamic perspective, emotional alterations of somatoform patients are interpreted as being caused by the unconscious repression of specific emotions to avoid interpersonal conflicts, which would cause strong negative affects (Bowlby, 1973; Waller and Scheidt, 2006). Somatizing patients are

thus unable to verbally express their emotional states whilst they still experience the somatic component related to their affective reaction (as symptom, Schur, 1955; Krystal, 1997; Beutel et al., 2008). In addition, increased attention to body sensations (in order to distract from interpersonal conflicts) plays an important role (Eriksen and Ursin, 2004; Nakao and Barsky, 2007; Witthöft and Hiller, 2010; de Greck et al., 2011).

Neurophysiologically, as was demonstrated in a previous paper by our group, pre-treatment somatoform disorder patients show diminished modulation of neuronal activity in several brain regions including the bilateral parahippocampal gyrus, the left amygdala, the left postcentral gyrus, the left superior temporal gyrus, and the left posterior insula, during emotional empathy (compared to healthy control subjects, de Greck et al. 2012). In particular, diminished neuronal activation of the parahippocampal gyrus is highly interesting, since other studies emphasized the crucial role of this region in the recall of autobiographical memories (Maguire, 2001; Niki and Luo, 2002; Rekkas and Constable, 2005; Gardini et al., 2006). Especially the retrieval of emotional memories activates the parahippocampal gyrus: For instance, Damasio and colleagues showed that the parahippocampal gyrus is involved in the induction of emotion by intentional retrieval of autobiographic emotional memory (Damasio et al., 2000). In addition, Smith and colleagues (2004) and Sterpenich and colleagues (2006) showed that the parahippocampal gyrus is also involved in the retrieval of emotional background contexts during the active recall of memorized neutral stimuli. Even more interesting, two studies found evidence showing that the parahippocampal gyrus is particularly involved in the processing of conflict related memories: Loughead and colleagues (2010) investigated brain activity during the recall of autobiographic relationship episodes, while also checking for relationship conflict. They found that activity in the parahippocampal gyrus was positively correlated with the degree of conflict related to autobiographical episodes. In complement to this, Schmeing and colleagues (2013) reported a deactivation of the parahippocampal cortex during free associations to conflict-related sentences (when compared to neutral sentences). Subsequent to the free association task, the authors included an unexpected memory recall task. They found that free associations to conflict-related sentences were more often forgotten when compared to free associations made to neutral sentences.

The diminished activation of the parahippocampal gyrus found during emotional empathy in somatoform disorder patients might hence reflect the disturbed retrieval of repressed emotional memories; accordingly, it might be a neurobiological correlate of repression.

Psychodynamic psychotherapy is an established therapy in the treatment of somatoform disorder (and other mental disorders, Leichsenring 2005; Gemeinsamer Bundesausschuss 2009). In the treatment of somatoform disorders, psychodynamic psychotherapy aims to increase the insight and acceptance of unconscious needs and emotional conflicts which underly the client's symptoms (Blagys and Hilsenroth, 2002; Leichsenring, 2005); thus, interpretations are a key instrument (Crits-Christoph et al., 1988). The process of "working through" aims to enable patients to utilize other (namely "healthier") coping strategies (Vaillant, 1977; Wöller and Kruse, 2010), leading to less somatic symptoms and a more satisfying life-style. Further aims of psychodynamic psychotherapy in somatoform disorder include enhancement of the mentalization function, improvement of affect perception and the reduction of medication abuse (Beutel et al., 2008).

Aim of this study was to investigate whether neuronal activity in the parahippocampal gyrus normalized after psychotherapy (mediated by the uncovering of repressed emotional memories). In addition, we were also interested, whether any of the other regions with diminished neuronal activity in the pre-treatment stage (i.e. the left amygdala, the left postcentral gyrus, the left superior temporal gyrus, and the left posterior insula) showed a normalization of neuronal activity in the post-treatment stage.

## METHODS

### ETHICAL APPROVAL

The study was ethically approved by the Institutional Review Board of the Otto-von-Guericke University of Magdeburg/Germany. After a detailed explanation of the study, all subjects gave informed consent. All subjects received financial compensation for their participation in the study. The study was conducted at the Otto-von-Guericke University of Magdeburg/Germany.

### PARTICIPANTS

We investigated 15 patients (8 females, 7 males; 14 right handed, 1 left handed; mean age: 42.6 years, 95%-confidence interval: 35.0–50.1 years) suffering from a somatoform disorder as ascertained by the Structured Clinical Interview for DSM-IV (German version: SKID, Wittchen et al. 1997). 11 of the 15 patients fulfilled criteria of an undifferentiated somatoform disorder (DSM-IV: 300.82), 2 of the 15 patients had a somatization disorder (DSM-IV: 300.81), and 2 of the 15 patients had a pain disorder (DSM-IV: 307.80). Leading symptoms of the pre-treatment patients included different forms of pain (e.g., back pain, neck pain, headache), abdominal disturbances (e.g., diarrhea, flatulence, abdominal pain), sexual dysfunctions, and others. All patients were recruited at the start of an inpatient psychotherapy. Patients were recruited from the Department of Psychosomatic Medicine and Psychotherapy of the Otto-von-Guericke-University Hospital in Magdeburg (9/15), from the Department of Psychotherapeutic Medicine of the Fachklinikum Uchtspringe (3/15), and from the Department of Psychosomatic Medicine and Psychotherapy of the AWO Hospital Jerichow (3/15). All patients underwent a second fMRI session at the end of their psychotherapy. The time difference between both scanning session was 58 days on average (95%-CI: 51–65 days; range: 38–80 days). During the first fMRI session, 5 patients were on psychotropic medication with duloxetine. During the second fMRI session, one patient continued with duloxetine and one other patient continued with duloxetine and trimipramine. In addition to the patient group, we also investigated 15 gender matched and age matched healthy control subjects (8 females, 7 males; 12 right handed, 1 left handed, 2 ambidextrous; mean age: 37.0 years, 95%CI: 34.4–45.4 years, $t_{(28)} = 0.614$; $p_{[\text{two-tailed}]} = 0.545$). This study included 15 patients, who were scanned in their pre-treatment stage and in their post-treatment stage. These 15 patients were taken out of a

larger population of 20 patients who were scanned in in the pre-treatment stage. Due to different reasons, however, 5 of those 20 patients were not scanned in their post-treatment stage. Drop out reasons included premature termination of psychotherapy (3/20), refusal to participate a second time (1/20), or inaccessibility after discharge (1/20).

In addition, this study is part of a larger trial where we compared patients with somatoform disorder patients pre and post multimodal inpatient psychodynamic treatment and healthy control subjects. Data obtained in this trial have already been presented in two previous papers of our group: In one study, we investigated 20 pre-treatment somatoform patients and 20 healthy subjects using the same paradigm (de Greck et al., 2012). In another study, we investigated 20 pre-treatment somatoform patients, 15 post-treatment somatoform patients, and 20 healthy subjects using a different paradigm (de Greck et al., 2011). In the here presented study, we focus on the effects of multimodal inpatient psychodynamic treatment on brain activity of somatoform disorder patients during emotional empathy—these data have not been published before.

### PSYCHOTHERAPEUTIC INTERVENTION

All patients participated in a standardized inpatient multimodal psychodynamic psychotherapy (henceforth "psychotherapy"), which was conducted as recently explained (Grabe et al., 2008; Haase et al., 2008; Huber et al., 2009; de Greck et al., 2011). The therapeutic setting was multimodal and included psychodynamic individual therapy, psychodynamic group therapy, medical therapy, and other therapeutic methods including music therapy, communicative movement therapy, art therapy, social therapy, and relaxation methods (see the Supplementary Material for a more detailed explanation of the therapeutic techniques). Psychotherapy aimed to improve the verbalization of emotional and interpersonal problems, to improve affect perception, and to enhance the understanding of intra-psychic and interpersonal conflicts underlying the patient's symptoms. (Leichsenring, 2005; Beutel et al., 2008; Grabe et al., 2008). Thereby, psychotherapy aimed to enable the patient to utilize a broader spectrum of coping strategies (Vaillant, 1977).

### PSYCHOLOGICAL SCALES

Several psychological measurements were used to investigate differences between patients and healthy subjects as well as differences between patients in the pre-treatment and post-treatment stage. Psychological data of healthy subjects were assessed only once.

Somatization was assessed by the respective sub-scale of the "Symptom Check List 90 - Revised Version" (SCL-90-R, German edition, Derogatis, 1977; Franke, 2002), a self-report questionnaire, which contains several sub-scales. SCL-90 somatization scores were collected from 15 of the 15 pre-treatment somatoform patients, 12 of the 15 post-treatment somatoform patients, and 14 of the 15 healthy control subjects.

Emotional awareness was tested by the German version of the well established self-report questionnaire "Toronto Alexithymia Scale - 20" (TAS-20, Bagby et al., 1994; Bressi et al., 1996). TAS-20 scores were collected from the 15 pre-treatment somatoform patients, the 15 post-treatment somatoform patients, and the 15 healthy control subjects.

Mood state and in particular depressive symptoms were assessed with a German edition of the "Beck Depression Inventory" (BDI, Beck et al., 1961). BDI scores were ascertained from the 15 pre-treatment somatoform patients, the 15 post-treatment somatoform patients, and the 15 healthy control subjects.

Emotion recognition abilities were tested using the "Tübinger Affekt Batterie" (TAB, Breitenstein et al. 1998), the German version of the "Florida Affect Battery" (FAB, Bowers et al., 1999). We applied four sub-tests of the TAB: TAB3 and TAB5, which use emotional face stimuli, TAB8a, which uses spoken emotional sentences to test for the ability to identify prosody and semantic content, and TAB8b, which uses spoken sentences as the TAB8a, but applies a number of incongruent auditory stimuli (i.e., sentences with different prosodic and emotional content). The average error rate of all sub-tests was included into the analysis. TAB scores were obtained from 15 pre-treatment somatoform patients, 14 post-treatment somatoform patients, and 12 healthy control subjects.

Statistical analyses of psychological scales included paired samples t-tests to investigate potential effects of psychotherapy, and Spearman-correlations to check for correlations between different scales. Spearman correlations (and not Pearson correlations) were used with regard to the non-linear characteristics of the different scales. We implemented one-tailed tests if we had a directed a priori hypothesis (e.g., improvement of symptom scores in the post-treatment stage), and two-tailed tests otherwise (e.g., differences between two conditions).

### PARADIGM

The paradigm contained a combination of two tasks, a reward anticipation task and an empathy task, which were separated from each other in a block wise manner. Here we report only results obtained from the empathy blocks; please, see our previous paper for results obtained during the reward anticipation paradigm (de Greck et al., 2011).

### EXPERIMENTAL DESIGN

Please also refer to our previous paper for an in depth description (de Greck et al., 2012). Subjects read detailed information about the paradigm and completed a couple of trial runs in order to familiarize with the experiment. In the scanner, stimuli were projected onto a matt screen via an LCD projector, which was visible through a mirror mounted on the head coil. During the *experiment* three empathy blocks were presented. Each *block* started with a short finger tapping task. Directly afterwards the actual empathy session began with the presentation of a short instruction, which lasted for 6 s. A total number of 40 empathy trials were then presented in a random order. After every 8 empathy trials, a short pause occurred, lasting for 6, 7, or 8 s duration; during pauses, the fixation cross was presented. At the end of each block, subjects were asked to rate their present feeling for contentedness as well as their impression of engagement in the empathy task, by moving a bar on a visual analogue scale. Each *trial* began with the display of an emotional face or a control

stimulus lasting for 5 s. Subjects were instructed to empathize with the presented emotional face, which was expressed by the phrase "please try to share the emotional state of the person shown." Immediately after the presentation of the emotional face, subjects were asked to rate their ability to empathize with the preceding picture by moving a bar of a visual analogue scale. Prior to the following empathy trial a short inter trial interval (lasting for 2 or 3 s) was presented. Facial stimuli expressing the emotion conditions anger, disgust, joy, and neutral emotional state were implemented. Smoothed pictures with unrecognizable contents served as control stimuli.

#### STIMULI

The emotional face stimuli were taken from two batteries: the "Japanese and Caucasian Facial Expressions of Emotion"-battery (JACFEE) and the "Japanese and Caucasian Neutral Faces"-battery (JACNeuF), both provided by Matsumoto and Ekman (Matsumuto and Ekman, 1988). Eight different facial stimuli of every emotion condition (anger, disgust, joy and neutral) were shown, resulting in 32 different stimuli. Stimuli depicted 16 Caucasian and 16 Japanese actors, half of them female, half of them male. 8 smoothed pictures with unrecognizable contents served as control stimuli. Subjects were instructed to rate the smallest empathy amount (zero) after a control stimulus was presented. During the whole experiment each stimulus was presented once in each block, and for three times during the entire experiment.

#### FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

##### *fMRI data collection*

fMRI data were collected in a 1.5T MR scanner (General Electric Sigma Horizon) using a standard circular polarized head coil. A stack of 23 slices was aligned parallel to the bicomissural plane. During functional runs 320 whole brain volumes were acquired (gradient echo EPI, $TR = 2$ s; $TE = 35$ ms; flip angle $\alpha = 90°$; Field of View $= 200 \times 200$ mm; slice thickness $= 5$ mm, inter-slice gap $= 1$ mm, spatial resolution $= 3.125 \times 3.125 \times 5$ mm). Additionally, a T1 weighted image of every subject was acquired (3D-FSPGR, 60 saggital slices; $TR = 8.8$ ms; $TE = 1.84$ ms; flip angle $\alpha = 30°$; Field of View $= 230 \times 173$ mm; slice thickness $=$ 2.8 mm, spatial resolution $= 2.8 \times 0.898 \times 0.898$ mm.

##### *fMRI data analysis*

Image processing and statistical analyses were carried out using the software package AFNI (http://afni.nimh.nih.gov/afni/, Cox 1996). The first five volumes of each functional run were discarded due to saturation effects. All functional images were slice-time corrected with reference to the acquisition time of the first slice and corrected for motion artifacts by realignment to the first volume. The images were spatially normalized to an AFNI-standard-EPI-template ("TT_EPI") and re-sampled to $3 \times 3 \times 3$ mm. Finally, all functional images were smoothed with an isotropic 6 mm full-width half maximum Gaussian kernel. T1-weighted images were normalized to a standard T1-template provided by AFNI ("TT_avg152T1"). For each subject, a voxel-wise whole brain analysis was implemented, and regressors of interest were calculated by the convolution of a gamma response function with the according stimulus time functions (Josephs et al., 1997). All relevant periods (i.e., empathy periods, evaluation periods, pauses, and the free interval at the end of each session) were included in the model. In addition, six movement parameters resulting from the motion correction procedure were included as regressors to account for head motion effects. Likewise, nine regressors for the 3rd degree polynomial model of the baseline of each block were included to control for baseline fluctuations. Contrast images were calculated for each subject by employing linear contrasts to the parameter estimates for the regressors of each event (Friston et al., 1995).

This was followed by a second level group statistic, based on two approaches:

Firstly, we performed a statistical analysis of parameter estimates extracted from regions of interest (ROIs). ROIs were taken from a previous paper of our group in which we used the same paradigm (and partially the same subjects, see above) and found diminished modulation of brain activity of pre-treatment somatoform patients in several brain areas (de Greck et al., 2012). When compared to healthy controls, pre-treatment somatoform patients had shown diminished modulation in their hemodynamic responses in 12 regions (i.e., two regions for the contrast ["anger" + "disgust" + "joy" + "neutral expression"] − "control", seven regions for the contrast "anger" − "control", and three regions for the contrast "joy" − "control"). Spherical ROIs (with a radius of 5 mm) were defined based on the coordinates of those 12 regions, and mean contrast values of the according contrasts were extracted. Paired samples *t*-tests were implemented to check for significant differences between pre-treatment and post-treatment somatoform patients. With regard to the high number (12) of statistical tests, we applied a Bonferroni-correction to account for the multiple testing problem. Only those statistical results with a *p*-value of less than $0.05/12 = 0.004$ were treated as significant results.

Secondly, we implemented a voxelwise second level random-effects analysis using paired samples *t*-tests (comparing the 15 somatoform patients in their pre-treatment stage and post-treatment stage) to identify brain regions which showed altered hemodynamic responses after psychotherapy. Again, we were only interested in contrasts, which had revealed a significant difference between pre-treatment somatoform patients and healthy control subjects in our previous study (de Greck et al., 2012) (namely ["anger" + "disgust" + "joy" + "neutral expression"] − "control," "anger" − "control," "joy" − "control"), whereas we did not investigate changes of hemodynamic responses after psychotherapy for the two other contrasts (namely "disgust" − "control" and "neutral expression" − "control"). To control for the multiple testing problem (Nichols and Hayasaka, 2003), we calculated family-wise error probabilities based on Monte-Carlo-simulations; in addition, small clusters with a size of $\leq$10 voxels were not respected. The anatomical localization and labeling of significant activations were assessed with reference to the standard stereotactic atlas of Talairach and Tournoux (1988) and by superimposition of the group contrast images on a mean brain generated by an average of normalized T1-weighted image of all patients.

Since 5 of the 15 patients were on psychotropic medication during either one or both scanning session, we implemented additional fMRI analyses including only data of those 10 participants who were without medication.

To check whether psychotherapy-induced reductions of somatic symptoms were associated with changes of hemodynamic responses in any of our regions of interest (i.e., the regions mentioned above plus significant regions of the voxelwise second level analysis), we implemented Spearman correlations of psychotherapy induced changes in SCL-90-somatization scores and psychotherapy induced changes of contrast values in the ROIs. We decided to implement Spearman correlations (and not Pearson correlations) with regard to the non-linear characteristics of the SCL-90-somatization scale.

Since we presented differences between pre-treatment somatoform patients and healthy subjects in a previous paper (de Greck et al., 2012), we here solely focused on the differences between pre-treatment and post-treatment somatoform patients. Data of healthy subjects are presented nevertheless for illustration purposes.

## RESULTS

### BEHAVIORAL RESULTS

#### *Psychological Scales*

As shown in **Figure 1**, psychotherapy had a significant effect on all applied outcome scales. *Somatization*, as assessed with the somatization sub-scale of the SCL-90-R, was significantly reduced after psychotherapy [$t_{(11)} = 3.564$; $p_{[\text{one-tailed}]} = 0.002^{**}$]. *Emotional awareness*, as assessed with the TAS-20, was significantly enhanced after psychotherapy [$t_{(14)} = 2.456$; $p_{[\text{one-tailed}]} = 0.014^{*}$]. In addition, *Mood state* was controlled using the BDI. After psychotherapy, we found a significant reduction of depressive symptoms [$t_{(14)} = 5.660$; $p_{[\text{one-tailed}]} = 0.001^{***}$]. Finally, *emotion recognition abilities*, which were assessed using the TAB, improved; error rates were significantly lower after psychotherapy [$t_{(13)} = 2.747$; $p_{[\text{one-tailed}]} = 0.008^{*}$].

When checking for correlations between different scales, we found that psychotherapy-induced reductions of SCL-90-somatization scores correlated with reductions of BDI-scores ($\rho_{[\text{Spearman}]} = 0.558$; $p_{[\text{one-tailed}]} = 0.025^{*}$). In addition, psychotherapy induced reductions of TAS-20 scores correlated with reductions of BDI-scores ($\rho_{[\text{Spearman}]} = 0.723$; $p_{[\text{one-tailed}]} = 0.001^{**}$). However, we did not find correlations of psychotherapy induced changes of SCL-90-somatization scores with changes in the TAS-20 ($\rho_{[\text{Spearman}]} = 0.323$; $p_{[\text{one-tailed}]} = 0.306$), of SCL-90-somatization changes with changes of error rates in the TAB ($\rho_{[\text{Spearman}]} = -0.145$; $p_{[\text{one-tailed}]} = 0.673$), of TAS-20 changes with changes of error rates in the TAB ($\rho_{[\text{Spearman}]} = -0.123$; $p_{[\text{one-tailed}]} = 0.674$), or ($\rho_{[\text{Spearman}]} = 0.139$; $p_{[\text{one-tailed}]} = 0.637$).

#### *Intra-scanner empathy ratings*

The $2 \times 4$ factorial ANOVA with "psychotherapy" ("pre-treatment" vs. "post-treatment") as first within-subjects factor and "emotion" ("anger," "disgust," "joy," and "neutral expression") as second within-subjects factor revealed a significant effect of "emotion" [$F_{(3,\ 112)} = 13.367$; $p < 0.001^{***}$], whilst we did not find significant effects for the factor "psychotherapy" [$F_{(1,\ 112)} = 1.142$; $p = 0.288$] or the interaction of "psychotherapy" × "emotion" [$F_{(3,\ 112)} = 0.586$; $p = 0.626$]. *Post-hoc t*-tests revealed, that empathy ratings for "anger" trials were significantly higher compared to "disgust" trials [$t_{(14)} = 4.715$; $p_{[\text{two-tailed}]} < 0.001^{***}$] and significantly lower compared to "joy" trials [$t_{(14)} = 5.924$; $p_{[\text{two-tailed}]} < 0.001^{*}$]. In addition, empathy ratings for "disgust" trials were significantly lower compared to "joy" trials [$t_{(14)} = 7.880$; $p_{[\text{two-tailed}]} < 0.001^{***}$], and empathy ratings for "neutral expression" trials were significantly lower compared to "joy" trials [$t_{(14)} = 6.479$; $p_{[\text{two-tailed}]} < 0.001^{***}$]. There were, however, no significant differences between empathy ratings for "anger" and "neutral expression" [$t_{(14)} = 0.234$; $p_{[\text{two-tailed}]} = 0.818$], and between empathy ratings for "disgust" and "neutral expression" [$t_{(14)} = 1.621$; $p_{[\text{two-tailed}]} = 0.127$].

### fMRI RESULTS

#### *ROI based comparison of hemodynamic responses*

In a previous paper, we found 12 brain areas (regions of interest, ROIs) with diminished modulation of hemodynamic responses in pre-treatment somatoform patients compared to healthy control subjects (de Greck et al., 2012). As shown in **Table 2**, we found significant improvement of hemodynamic responses

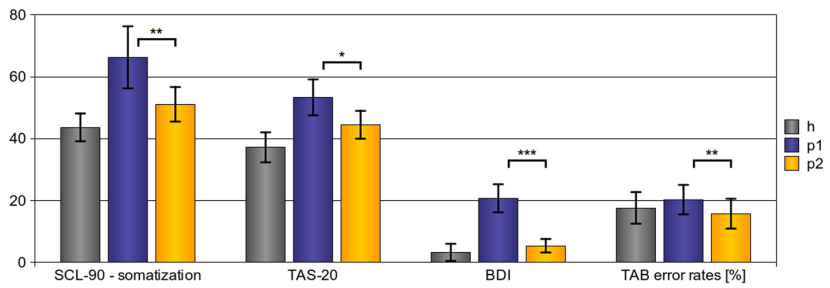


**FIGURE 1 | Behavioral results—effects of psychotherapy.** After psychotherapy we observed a significant reduction of somatization severity (SCL-90 - somatization scores), to enhanced emotional awareness (TAS-20 scores), and to a reduction of depressive symptoms (BDI scores). In addition, emotion recognition abilities improved after psychotherapy as shown by a significant reduction of error rates in the TAB. (Explanations: *h*, *p*1, and *p*2 refer to the scores of healthy subjects (h), pre-treatment somatoform patients (*p*1), and post-treatment somatoform patients (*p*2); error bars indicate the 95%-confidence-interval; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, with regard to one-tailed *t*-tests.)

after psychotherapy in 6 of the 12 regions—all for the contrast "anger"—"control."

### *Voxel-wise whole brain analysis*

In addition to the above described ROI based approach, we also implemented a voxel-wise whole brain statistical analysis to identify brain regions with altered hemodynamic responses. As presented in **Table 3** and **Figure 2**, four regions showed a significant effect of psychotherapy on hemodynamic modulation: The bilateral parahippocampal gyrus and the left inferior temporal gyrus showed increased modulation of hemodynamic responses after psychotherapy, the left putamen had diminished modulation of hemodynamic responses after psychotherapy.

**Table 1 | Intra-scanner empathy ratings.**

| Condition | *h* | *p1* | *p2* |
|---|---|---|---|
| Anger | 62.6 ± 10.8 | 62.8 ± 11.8 | 63.9 ± 10.5 |
| Disgust | 61.2 ± 12.1 | 56.9 ± 12.2 | 56.8 ± 10.2 |
| Joy | 82.8 ± 8.5 | 86.7 ± 5.3 | 81.3 ± 7.6 |
| Neutral expression | 62.0 ± 9.6 | 69.2 ± 8.4 | 59.8 ± 9.9 |

*(Abbreviations: h, p1, and p2 refer to the mean empathy rating of the according condition, where h indicates data of healthy subjects, p1 indicates data of pre-treatment somatoform patients, and p2 indicates data of post-treatment somatoform patients; ± indicates the 95%-confidence-interval).*

### *Correlation of psychotherapy induced effects*

We were interested, whether psychotherapy induced alleviations of somatic symptoms (as ascertained with the SCL-90-somatization sub-scale) correlated with psychotherapy induced changes of hemodynamic responses in any of our ROIs. With regard to those ROIs which had previously shown diminished modulation of hemodynamic responses in pre-treatment somatoform patients (i.e., ROIs listed in **Table 1**), we did not find any significant correlations under reasonable statistical thresholds (Spearman correlations, $p_{[\text{two-tailed}]} < 0.05$). With regard to the ROIs found in the voxel-wise analysis (i.e., ROIs listed in **Table 2**), we found only one significant correlation: the reduction in the SCL-90 somatization scores induced by psychotherapy correlated with the reduction of hemodynamic responses in the left putamen ($\rho = 0.811$; $p_{[\text{one-tailed}]} = 0.001^{**}$).

### *Control for potential effects of the psychotropic medication*

Since 5 of the 15 patients were on psychotropic medication during either on one or both scanning sessions, we implemented two additional fMRI analyses (i.e., an additional ROI-based approach and an additional voxelwise approach) including only data of the 10 patients without medication. These results support the

**Table 2 | Effect of psychotherapy on hemodynamic responses—ROI based approach.**

| Region | | Coordinates | | | fMRI contrast values | | | Psychotherapy effect |
|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | *h* | *p1* | *p2* | *p2 > p1* |
| ***All emotions (["anger"+ "disgust" + "joy" + "neutral"] − "control")*** | | | | | | | | |
| Right | parahippocampal gyrus | 30 | 54 | −3 | −0.51 ± 1.77 | −5.53 ± 2.25 | −4.26 ± 2.60 | $t_{(14)} = 0.670$; $p_{[\text{one-tailed}]} = 0.257$ |
| Left | amygdala | −24 | −3 | −24 | 0.50 ± 0.87 | −0.59 ± 1.54 | −0.27 ± 1.47 | $t_{(14)} = 0.355$; $p_{[\text{one-tailed}]} = 0.364$ |
| ***Anger ("anger" − "control")*** | | | | | | | | |
| Left | Postcentral gyrus | −15 | 39 | 66 | 0.60 ± 0.70 | −0.83 ± 0.83 | 0.41 ± 0.84 | $t_{(14)} = 2.042$; $p_{[\text{one-tailed}]} = 0.030^{*}$ |
| Left | Superior temporal gyrus | −33 | −15 | −27 | 1.05 ± 0.60 | −0.91 ± 1.03 | 0.23 ± 0.94 | $t_{(14)} = 1.899$; $p_{[\text{one-tailed}]} = 0.039^{*}$ |
| Left | Parahippocampal gyrus | −33 | 18 | −24 | 0.78 ± 0.60 | −0.39 ± 0.52 | 0.19 ± 0.81 | $t_{(14)} = 1.914$; $p_{[\text{one-tailed}]} = 0.038^{*}$ |
| Right | Parahippocampal gyrus | 18 | 21 | −15 | 1.20 ± 0.91 | −0.92 ± 0.98 | 0.77 ± 0.63 | $t_{(14)} = 3.829$; $p_{[\text{one-tailed}]} < 0.001^{***\dagger}$ |
| Left | Posterior insula | −36 | 33 | 15 | 0.66 ± 0.50 | −0.56 ± 0.62 | 0.12 ± 0.64 | $t_{(14)} = 2.151$; $p_{[\text{one-tailed}]} = 0.025^{*}$ |
| Left | Amygdala | −21 | −3 | −21 | 1.24 ± 0.83 | −0.57 ± 1.06 | 0.37 ± 0.77 | $t_{(14)} = 1.621$; $p_{[\text{one-tailed}]} = 0.064^{(*)}$ |
| Left | Cerebellum | −36 | 81 | −24 | 3.64 ± 1.34 | 0.97 ± 1.34 | 2.72 ± 1.40 | $t_{(14)} = 3.633$; $p_{[\text{one-tailed}]} = 0.001^{**\dagger}$ |
| ***Joy ("joy" − "control")*** | | | | | | | | |
| Right | Parahippocampal gyrus | 30 | 54 | −3 | 0.29 ± 0.42 | −1.57 ± 0.74 | −1.07 ± 0.77 | $t_{(14)} = 0.919$; $p_{[\text{one-tailed}]} = 0.187$ |
| Right | Cerebellum | 33 | 84 | −27 | 3.70 ± 1.40 | 0.31 ± 1.25 | 0.65 ± 1.43 | $t_{(14)} = 0.628$; $p_{[\text{one-tailed}]} = 0.270$ |
| Right | Cerebellum | 21 | 87 | −30 | 3.35 ± 1.44 | 0.47 ± 0.95 | 0.55 ± 1.01 | $t_{(14)} = 0.159$; $p_{[\text{one-tailed}]} = 0.438$ |

*In a previous study of our group, 12 regions of interest (ROIs) had shown significantly reduced modulation of hemodynamic responses during the same paradigm in pre-treatment somatoform disorder patients. Here, we investigated whether contrast values extracted from these ROIs showed a significant normalization after psychotherapy. In six ROIs, we found a significant enhancement of hemodynamic modulation after psychotherapy. After correction for multiple comparisons using a Bonferroni-correction, two ROIs (i.e., the right parahippocampal gyrus and the left cerebellum) showed a significant effect. (Abbreviations: x, y, and z refer to the Talairach coordinates of the regions; h, p1, and p2 refer to the contrast value of the according contrast, where h indicates data of healthy subjects, p1 indicates data of pre-treatment somatoform patients, and p2 indicates data of post-treatment somatoform patients; ± indicates the 95%-interval; (*): p < 0.1; *: p < 0.05; **: p < 0.01; ***: p < 0.001; †: p < 0.004, this indicates a significant effect after controlling for multiple comparisons using a Bonferroni-correction.)*

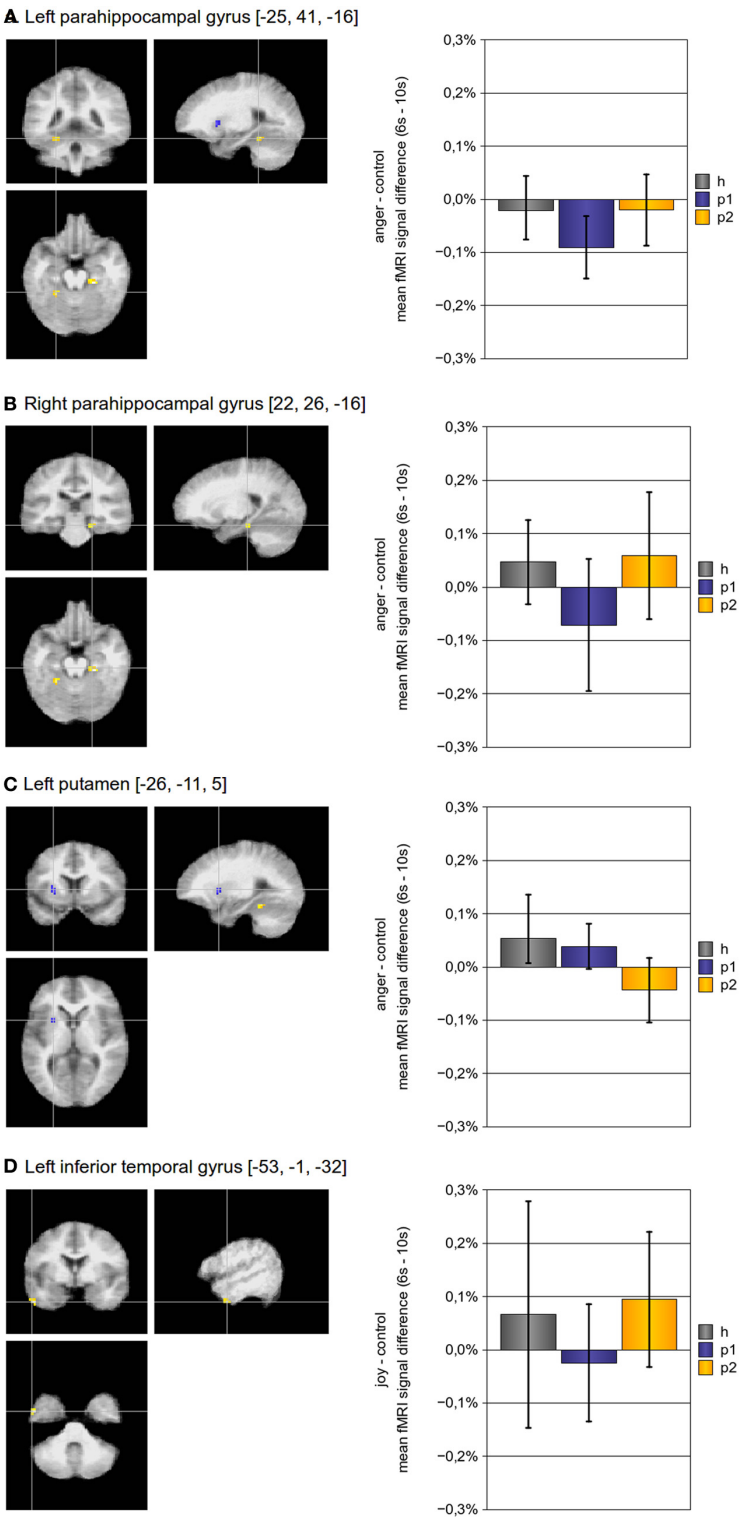


**FIGURE 2 | Brain activity modulated by multimodal psychotherapy.** Using a voxel-wise whole brain analysis, we found three regions for the contrast "anger"-"control" and one for the contrast "joy"-"control", which had a significant increase (bilateral parahippocampal gyrus, left inferior frontal cortex) or decrease (left putamen) of hemodynamic modulation after psychotherapy. The *p*-threshold was set to $p_{[uncorrected]} \leq 0.001$; only clusters with a cluster size of more than 10 voxels were taken into account. (Abbreviations: *h*, *p*1, and *p*2 refer to the mean fMRI signal difference of the according contrast, where *h* indicates data of healthy subjects, *p*1 indicates data of pre-treatment somatoform patients, and *p*2 indicates data of post-treatment somatoform patients; error bars indicate the 95%-confidence-interval).

**Table 3 | Effect of psychotherapy on hemodynamic responses—voxel-wise whole brain analysis.**

| Region | | Coordinates | | | Peak *t* value | Cluster size | FWE value | Effect |
|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | | | |
| ***All emotions (["anger"+ "disgust" + "joy" + "neutral"] − "control")*** | | | | | | | | |
| No | Region | | | | | | | |
| ***Anger ("anger" − "control")*** | | | | | | | | |
| Left | Parahippocampal gyrus | −25 | 41 | −16 | 5.560 | 11 | 0.998 | p2 > p1 |
| Rightt | Parahippocampal gyrus | 22 | 26 | −16 | 6.130 | 11 | 0.998 | p2 > p1 |
| Left | Putamen | −26 | −11 | 5 | 5.322 | 11 | 0.998 | p2 < p1 |
| ***joy ("joy" − "control")*** | | | | | | | | |
| Left | Inferior temporal gyrus | −53 | −1 | −32 | 6.173 | 12 | 0.960 | p2 > p1 |

*We implemented a voxel-wise whole brain analysis to identify brain regions with significant changes of hemodynamic modulation for the contrasts all emotions (["anger"+ "disgust" + "joy" + "neutral"] − "control"), anger ("anger" − "control"), and joy ("joy" − "control"). (Abbreviations: x, y, and z refer to the Talairach coordinates of the center of mass of the regions; peak t value refers to the t value of the peak voxel in the cluster; cluster size refers to the number of voxels which survived threshold masking at $p_{[uncorrected]} \leq 0.001$; FWE value describes the probability, that a cluster of the given size would appear as a false positive result in a contrast of the given smoothness; effect refers to an increase (p2 > p1) or a decrease (p2 < p1) of hemodynamic responses after psychotherapy.)*

view that modulation of hemodynamic responses in the left superior temporal gyrus, right parahippocampal gyrus, left posterior insula, and left cerebellum (ROI-based approach), as well as in the in the bilateral parahippocampal gyrus, left putamen, and left inferior frontal gyrus (voxelwise approach) are not caused by the effects of psychotropic medication. Please see the Supplementary Material for a detailed presentation of the according results.

## DISCUSSION

### SUMMARY OF FINDINGS

Somatoform disorder patients in a pre-treatment stage show diminished modulation of hemodynamic responses during emotional empathy in several brain areas, including the bilateral parahippocampal gyrus, left amygdala, left postcentral gyrus and others; this was reported in a previous paper by our group (de Greck et al., 2012). Here, we investigated whether brain activity normalized after multimodal psychodynamic psychotherapy. Psychotherapy was successful as demonstrated by a significant reduction of somatization symptoms (based on the SCL-90 somatization sub-scale), alexithymia symptoms (TAS-20), and depressive symptoms (BDI). In addition, psychotherapy led to significant reduction of error rates in an emotion recognition test (TAB).

The analysis of psychotherapy induced changes of brain activity was implemented using two approaches: a region of interest (ROI) based approach and a voxel-wise whole brain analysis. Both analyses came to the matching results that brain activity in the bilateral parahippocampal gyrus during empathy with anger normalized after psychotherapy. With regard to the ROI based analysis, we found that brain activity in almost all of those regions which had shown diminished modulation of hemodynamic responses in the pre-treatment stage for the contrast "empathy with anger" − "control" normalized after psychotherapy. Regions with a normalization after psychotherapy included the left postcentral gyrus, left superior temporal gyrus, left posterior insula, left amygdala (statistical trend), left cerebellum, and the above mentioned bilateral parahippocampal gyrus.

However, none of those regions which had shown diminished modulation of hemodynamic responses of pre-treatment somatoform patients during other contrasts (namely "empathy with all emotions" − "control," and "empathy with joy" − "control"), showed a normalization of hemodynamic responses after psychotherapy.

With regard to the voxel-wise whole brain analysis, we found three regions, which had a significant change in neuronal activity after psychotherapy for the contrast "empathy with anger" - "control" (the bilateral parahippocampal gyrus, and the left putamen), and one region for the contrast "empathy with joy" − "control" (the left inferior temporal gyrus). Interestingly, the left putamen showed *less* modulation of hemodynamic responses after psychotherapy, whereas modulation was increased in all other regions. In addition, the left putamen was the only region in which reduction of hemodynamic responses was correlated with the reduction of somatic symptoms after psychotherapy (over all patients).

### PSYCHODYNAMIC MECHANISMS IN SOMATOFORM DISORDER

From a psychodynamic perspective, the development of somatoform symptoms can be understood as malfunctioning of secondary process mechanisms concerning the handling of emotional conflicts which leads to "resomatization" (i.e., the appearance of somatoform symptoms as "concomitants" or "equivalents" of affective tensions, Schur, 1955). In other words: unreleased affective tensions caused by unconscious emotional conflicts induce the corresponding somatic responses (which appear as somatic symptoms), whereas the corresponding affective component is repressed and can not be experienced (Lipowski, 1988; Hoffmann et al., 2004). In this regard, somatization (i.e., the development of medically unexplained somatic symptoms, Lipowski, 1988) is either seen as a defense mechanism itself (Bond et al., 1983; Lipowski, 1988), or as a correlate of immature defense styles (Nickel and Egle, 2006). In addition to

emotional conflicts, the experience of overwhelmingly strong negative emotional reactions, which may occur for instance as a response to childhood adversities, can lead to a breakdown of secondary process thinking and a malfunction of mature defense mechanisms (Nickel and Egle, 2001). As a consequence, these patients are prone to develop reduced emotional awareness as correlate of the repressed emotional component, and somatic symptoms as equivalents of affective tensions (Krystal, 1997). Indeed, there is a strong link between childhood adversities and adult somatization (Spitzer et al., 2008).

### HOW DOES PSYCHOTHERAPY HELP PATIENTS WITH SOMATOFORM DISORDERS?

Psychodynamic psychotherapy, as it was applied in our study, aims to increase the insight and acceptance of unconscious emotions, needs and conflicts (Blagys and Hilsenroth, 2002; Leichsenring, 2005), and to enable patients to gain "mastery over his or her repressed wishes, desires, fears, or anxieties" (Blagys and Hilsenroth, 2002). Regarding this, the development of more mature defense mechanisms and coping strategies is a core aim (Vaillant, 1977). Further treatment goals include the establishment of a psychosomatic disease model, the enhancement of affect differentiation, a better understanding of underlying stresses, and the reduction of medication abuse (Beutel et al., 2008). In the case of somatoform disorder, successful psychotherapy leads to enhanced secondary process thinking, more mature defense mechanisms, improved "desomatization", and decreased somatic symptoms.

The reduction of somatic symptoms after psychotherapy in our study reflects a decreased use of somatization (i.e., improved "desomatization"). Improved emotion recognition after psychotherapy is probably caused by the uncovering of repressed emotional conflicts and emotional needs, which hampered emotion recognition in the pre-treatment stage.

### NEUROPHYSIOLOGICAL MECHANISMS IN SOMATOFORM DISORDER

The bilateral parahippocampal gyrus seems to play a key role in the affective dysfunctions of somatoform disorder (in particular in the processing of angry facial stimuli), since we found a significantly diminished modulation of hemodynamic responses in this area in the pre-treatment stage (de Greck et al., 2012) and a significant improvement after psychodynamic psychotherapy. Interestingly, the parahippocampal gyrus is involved in the recall of autobiographical memories (Maguire, 2001; Niki and Luo, 2002; Rekkas and Constable, 2005; Gardini et al., 2006), in particular the retrieval of emotional memories (Damasio et al., 2000), or emotional background informations (Smith et al., 2004; Sterpenich et al., 2006). In addition, the recall of conflictual memory content activates the parahippocampal gyrus (Loughead et al., 2010), and it is less activated during free associations to conflict-related themes (Schmeing et al., 2013).

### AFFECTIVE PROCESSING IN SOMATOFORM DISORDER AND THE EFFECT OF PSYCHOTHERAPY

High co-morbidity of somatoform disorder and alexithymia (i.e. diminished awareness of own and other's emotional processes) has been reported by various investigators (Bach and Bach, 1996; Bankier et al., 2001; Duddu et al., 2003; Grabe et al., 2004; Burba et al., 2006; Bailey and Henry, 2007; Mattila et al., 2008; Wood et al., 2009). From a psychodynamic point of view, the link between alexithymia and somatization is explained by a breakdown of secondary process coping with emotional conflicts, followed by the repression of the corresponding affective component and the experience of the somatic component as unexplained body symptoms (Schur, 1955; Lipowski, 1988; Hoffmann et al., 2004). Our data suggests that the parahippocampal gyrus, a region known for its involvement in the processing of autobiographic emotional memories, might be a neural key correlate of this process. In our study, we investigated brain activity during the intentional empathic processing of facial emotions. The process of intentional emotional empathy rests upon emotional sub processes which include emotional and cognitive empathy, emotion recognition, affective and cognitive mentalizing and the processing of autobiographical memory (Shamay-Tsoory, 2011). In order to empathize with somebody else, it is essential to generate a congruent emotional image of the target's emotional state within oneself (Preston and de Waal, 2002). Besides emotional contagion (Preston and de Waal, 2002; Shamay-Tsoory, 2011), this process relies on the recall of autobiographic memory traces (Damasio et al., 2000): If I want to understand from your face, what you feel, and intentionally want to share your emotional state, I may try to recall own memory traces which previously led to a similar emotional response in myself. This process involves the retrieval of emotional autobiographic memory and induces activity in the parahippocampal gyrus. In the case of somatoform disorder, however, it is assumed that overwhelmingly strong emotional conflicts led to a breakdown of emotional processing and a suppression of the corresponding memory traces, resulting in a diminished modulation of the parahippocampal gyrus during emotional empathy. Psychodynamic psychotherapy, however, can restore the retrieval of repressed autobiographic memories, which leads to increased modulation of the parahippocampal gyrus.

### PSYCHOANALYTICAL NEUROSCIENCE

We believe our study is a fine example, which demonstrates how neuroscience can benefit from psychoanalysis. Our main finding (i.e., pre-treatment somatoform disorder patients show diminished modulation of neuronal activity in the parahippocampal gyrus during the empathic processing of angry faces; this pattern normalizes after psychotherapy) fits well to psychoanalytical concepts of somatoform disorder. In fact, it is hard to explain our findings without referencing to psychodynamic concepts, which relate somatoform disorder to repressed emotional memories.

When it comes to the investigation of the neuronal underpinnings of complex emotional processing (and in particular its dysfunctions in psychosomatic diseases such as somatoform disorder) psychoanalytical concepts may provide a profound base to interpret neuroscientific findings.

## LIMITATIONS

Our psychotherapeutic intervention was "multimodal", i.e., it included a variety of different therapeutic techniques. Hence, we can not conclude for sure that increased emotional insight in

formerly repressed conflicts caused the reduction of symptoms and normalization of brain activity (and not for instance other therapeutic variables such as decreased depression).

Even more important, with the existing design, we can not for sure conclude that changes observed in the pre-post comparison are indeed caused by psychotherapy since they might be related to other factors, such as for instance retest effects, spontaneous remission, or in particular, regression to the mean effects (Barnett et al., 2005). To control for these potential confounds it would have been essential to scan a second control group consisting of somatoform patients, who would have been also scanned for two times without participation in psychotherapy.

However, the fact that we found reduced neuronal activity in the *bilateral* parahippocampal gyrus in the pre-treatment stage, and normalized activity in the *bilateral* parahippocampal gyrus in the post-treatment stage, supports the view that these activations are not related to regression to the mean effects (because it would be rather improbable that regression to the mean effects lead to bilateral effects in the same brain region).

## CONCLUSION

Our results are in accordance with the conclusion that the repression of emotional memories, which occurs in somatoform disorder in order to defend against overwhelmingly strong emotions, can neurophysiologically be understood in terms of diminished activation of the parahippocampal gyrus. Psychotherapeutic measures aim to increase emotional insight and to accept repressed feelings and emotional memories. After psychotherapy, somatoform patients reported less symptoms and showed stronger neuronal activity in the parahippocampal gyrus. Our results support the assumption that increased access to repressed emotional memories is related to increased neuronal activity of the parahippocampal gyrus.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/Human_Neuroscience/10.3389/fnhum.2013.00410/abstract

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# What would be the benefits of a collaboration between psychoanalysis and cognitive neuroscience? The opinion of a neuroscientist

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## CONTEXT OF DEVELOPMENT AND GUIDING PRINCIPLES OF PSYCHOANALYSIS AND COGNITIVE NEUROSCIENCE

Psychoanalysis was conceived and developed for clinical purposes at the beginning of the 20th century. Freud's main goal was to treat neurotic patients and psychotic patients. As a consequence of this great enterprise he developed a theory to explain the functioning of the human mind. A critical contribution of his work was the theory of the unconscious and the proposal that even if unconscious, a representation can influence a subject's behavior. Freud believed that unconscious thoughts and feelings may cause a patient to experience life difficulties and/or maladjustments. He proposed that the process of freeing unconscious thoughts could help a patient gain insight into and ultimately improve his/her situation. Therefore, Freud developed techniques to decode unconscious images, and to free them through patient insight (e.g., Freud, 1901).

Cognitive neuroscience is a rather young discipline. It was developed in the 1980's and has been strongly linked to the advancement of neuroimaging techniques (mainly positron emission tomography, PET, and functional magnetic resonance imaging, fMRI). The main goal of this discipline is to understand the functioning of the human brain/psyche. A consequence of this great enterprise has been, and hopefully will be, clinical applications. Cognitive neuroscience is fundamentally interested in processes/effects which can be found in several subjects rather than in the specific functioning of single subjects. Of importance, at the moment, this discipline does not provide a consensual and comprehensive theory of the human mind. It has, nevertheless, demonstrated that neuroscientific results can help to shape psychological theories or to disentangle between psychological theories (e.g., Henson, 2005; Poldrack, 2006; Legrand and Ruby, 2009).

## PITFALLS AND GAPS IN THE TWO DISCIPLINES SHOWING THE NEED FOR A BILATERAL COLLABORATION

Psychoanalysis is considered by many scientists as an unscientific, an thus untrustworthy discipline. Psychoanalysis needs then to improve its credibility. A collaboration with a scientific discipline such as cognitive neuroscience could certainly help to achieve this aim. In addition, at the theoretical level, one cannot exclude that the investigation of the neurophysiological correlates of psychoanalytical concepts (e.g., Kaplan-Solms and Solms, 2000) could result in a better understanding of the links between some psychoanalytical concepts, as neurophysiological results have already resulted in a better understanding of concepts from experimental psychology (e.g., Henson, 2005; Poldrack, 2006; Legrand and Ruby, 2009).

A current weakness of cognitive neuroscience is to ignore some important brain/mind properties/characteristics, such as (1) what is important to the individual subjects, or in other words the notion of "meaning" in the Freudian sense, (2) the subject's history and preferences, (3) the notion of affective unconscious which is closely related to the Freudian unconscious, (4) the unconscious memory of experienced events (UMEE), which refers to the memory of an episode or a scene that cannot be consciously recollected. All of these issues are at the core of our intimate mind; they are the foundation of our identity. One cannot expect to propose a comprehensive theory of the human mind if neglecting these issues. A collaboration with psychoanalysis, which could be considered as a "science" of singularity, appears then providential to help finding solutions to address private issues in cognitive neuroscience (Ruby, 2011).

## WHAT WOULD BE THE BENEFITS OF A COLLABORATION? THE CASE OF UMEE

### UMEE ARE NEGLECTED IN COGNITIVE NEUROSCIENCE

In cognitive neuroscience, the dominant theory of memory states that long-term memory can be either explicit or implicit. These two types of memory are often referred to as declarative (composed of episodic and semantic memory) and procedural memory or the "knowing what" and the "knowing how." This well-used way of naming explicit and implicit memories show that the notion of "knowing what implicitly/unconsciously" is not emphasized at the theoretical level. It is also true at the experimental level. The issue of UMEE in particular has been barely investigated in cognitive neuroscience. Rather, this concept is often ignored and possibly denied which has important consequences on the interpretation of results and thus theories of the brain/mind.

The consideration of UMEE has been lacking for example in research

investigating memory and the self, as illustrated by the article of Klein and Gangi in the Annals of the New York academy of sciences (Klein and Gangi, 2010). In this study, the authors aimed to better understand the link between the different types of self-related memory systems, by investigating the representation of self-personality traits in patients with amnesia. They report results showing that some patients with episodic amnesia (with traumatic or developmental etiologies) can, despite their amnesia, update the representation of their own personality traits. For Klein and Gangi, these cases showed that episodic and semantic memory systems were separate and independent. Interestingly, they also considered at some point the possibility that UMEE may participate in the updating of personality traits since they wrote "K.C. not only had access to semantic knowledge of his own personality traits, but he was also able to acquire new knowledge about his personality. Yet this updating occurred without his being able to episodically recollect any information about the behavioral events on which this updating presumably was based." Unfortunately, the authors did not develop this point and did not discuss the hypothesis of the updating of personality traits based on the UMEE. However, according to their results, one cannot exclude this possibility. How could one otherwise explain their results? The most likely hypothesis is that a semantic representation of one's own personality is elaborated using memories (conscious or unconscious) of past episodes of one's own life, and especially episodes involving human interactions. Klein and Gangi did not provide an alternative explanation but argued against this hypothesis by stating that they "devoted a substantial amount of [their] research (consisting in multiple methods—for example, priming techniques, transfer appropriate processing, the method of reversed association[39, 55]) to show that exemplar-based self-knowledge is not activated (consciously or unconsciously) when participants perform semantic judgments about the self.[29, 35]." However, these results do not exclude the possibility that UMEE participate in the formation of semantic knowledge even if it is not activated during semantic tasks.

UMEE is also barely considered in the field of dream research. Memory (be it conscious or not) is the main source of information available during sleep. Previous studies have looked for episodic recall in the content of dreams (e.g., Fosse et al., 2003), but to my knowledge, no studies have investigated whether UMEE show up in dream content or not. Investigating autobiographical memory in the elderly, Grenier et al. (2005) showed that dreams could bring back very old memories and especially memories from adolescence. Interestingly, these results were not explained by a recent reminiscence of these remote memories because "the participants indicated that to the best of their knowledge, they had not thought of or talked about the different elements experienced in their dreams since the time of the original experience." This type of memory may be closely related to unconscious memory (repressed or not) because according to the participants, the episode recalled in the dream had not reached consciousness since this episode actually happened. It seems thus fairly possible that dreams could bring unconscious memories or representations to consciousness, but this has not yet been tested.

## UMEE ARE AT THE CORE OF PSYCHOANALYTIC PRACTICES

Even if they are difficult to uncover and confirm, UMEE does exist. Here is a tragic example from the French news from the winter of 2012 (e.g., Sud Ouest 29/02/2012; Le Monde 03/03/2012). A women living in Lyon, France (Zahia H.) recalled the memory of being raped and assaulted 37 years prior, in 1973, upon awakening from general anesthesia in 2010. The surgery (one of many previous surgeries) was indicated to treat disabilities caused by this aggression. Thirty seven years ago, Zahia awoke from a coma induced by the episode and had no memory of the rape and the head injury which she had sustained. Zahia's mother decided not to tell her what had occurred. Thirty seven years after, when Zahia recalled the memory of this tragic episode her mother was dead.

This case demonstrates the existence of unconscious memories of important experiences (the facts can be verified). One can easily intuit reading this story, that memories, even if implicit/unconscious, may influence behavior (for example, unexplained fear in particular situations) and play an important role in a subject's life, as hypothesized by Freud. In support of this single case, Mitchell (2006) managed to produce experimental results showing the existence of long-lasting unconscious memory of images. He demonstrated that pictures presented 1–3 s could induce a priming effect 17 years after presentation, even in subjects who reported no conscious recollection of their participation in the original laboratory session.

Currently, cognitive neuroscience cannot easily explain the recovery of a memory 30 or 40 years later. By contrast, this phenomenon can be explained from a psychoanalytic perspective (When I previously described Zahia's case in a conference, René Roussillon, psychoanalyst and professor of psychology at the University of Lyon, predicted that the mother of Zahia was dead when she recovered the memory of the rape even though I did not mention this fact). This comes as no surprise since the core of psychoanalytic practice is centered on unconscious memories or representations that induce life difficulties and/or maladjustment and on the means to free them.

## WHAT WOULD BE THE BENEFIT OF A COLLABORATION BETWEEN PSYCHOANALYSTS AND NEUROSCIENTISTS ON UMEE

On the one hand, UMEE is a component that can be easily incorporated into a theoretical model of memory in cognitive neuroscience; on the other hand, this type of memory plays a central role in psychoanalysis since conflicts and trauma may lead (via repression or not) to the creation of UMEE. Therefore, the UMEE (resulting from repression or not) could be a strong convergence point between psychoanalysis and cognitive neuroscience, which may help to built bridges between the two disciplines. Below, possible benefits of a collaboration between psychoanalysis and cognitive neuroscience on UMEE.

### *New hypotheses on the functioning of memory systems in cognitive neuroscience*

Adding a psychoanalytical perspective to reflections on cognitive neuroscience

experiments may result in new hypotheses. This can be illustrated by the two examples described above. First, the hypothesis of the possible participation of UMEE in the formation of semantic knowledge about the self derives from a psychoanalytical perspective on the functioning of the mind/brain. Testing this hypothesis would help to better understand the formation of the semantic representation of one's personality traits, which according to Klein and Gangi (2010), is still a mystery: "Of the systems of self we have examined, the semantic self-knowledge system seems the most resilient in the face of the cognitive chaos resulting from developmental and/or environmental damage to the brain. This is both an empirical fact and a mystery for which we have, at present, no explanation." Second, according to Freud (e.g., Freud, 1901), unconscious representation may surface during dreams. Collaboration with psychoanalysts could assist in the design of experiments to test this hypothesis. For example, one could try to use the free association method to test whether free association initiated from the words of a dream would lead to UMEE. The results would help to elucidate whether dreams are indeed the royal road to the unconscious and could also have important implications for theories of sleep, dreams and memory.

### *New paradigms to test unexplored issues in cognitive neuroscience*

The absence of consideration of the UMEE in cognitive neuroscience is certainly due to the difficulty in investigating such private issue using an experimental approach. Psychoanalysts who work to make unconscious representations conscious may be helpful in developing methods to address this issue in cognitive neuroscience. Previous interdisciplinary work proves that novel paradigms can enable a scientific investigation of concepts that are seemingly impossible to explore. For example, Howard Shevrin, psychoanalyst and Professor of Psychology at The University of Michigan, developed shrewd paradigms to investigate unconscious processes at the experimental level. Using event related potentials and a free association method, his team identified neurophysiologic markers of subliminal perceptions and showed that subliminal images were processed in a complex and associative way (Shevrin and Fritzler, 1968). Using similar means (mild electric shock presented 800 ms after images or words presented subliminally) he also demonstrated that aversive conditioning can occur unconsciously (Shevrin, 2001). These results had a great impact on the neuroscientific community and precipitated an interest in unconscious processes.

### *Optimize therapeutic means in the psychoanalytic practice*

The investigation of UMEE in cognitive neuroscience should result in a better understanding of the context of formation (repression or not) and the neurophysiological basis of UMEE (possibly dependent on the context of formation). Theoretically, this should help to optimize the therapeutic means to act on or free such memories.

## CONCLUSION

Even if difficult, unconscious processes, private issues (preferences, history, what matters for a subject.) and, more generally, psychoanalytic concepts have to be addressed at the experimental level to achieve a comprehensive theory of the human mind. Another great benefit of such an endeavor would be to provide objective arguments and allow a constructive and scientific debate about whether Freudian or psychoanalytical concepts are plausible and useful. In other words, a collaboration between psychoanalysis and cognitive neuroscience may be the best way to escape from the sterile and counterproductive hostility between the disciplines and to move forward together in order to benefit science and medical practices.

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# Subliminal unconscious conflict alpha power inhibits supraliminal conscious symptom experience

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Our approach is based on a tri-partite method of integrating psychodynamic hypotheses, cognitive subliminal processes, and psychophysiological alpha power measures. We present ten social phobic subjects with three individually selected groups of words representing unconscious conflict, conscious symptom experience, and Osgood Semantic negative valence words used as a control word group. The unconscious conflict and conscious symptom words, presented subliminally and supraliminally, act as primes preceding the conscious symptom and control words presented as supraliminal targets. With alpha power as a marker of inhibitory brain activity, we show that unconscious conflict primes, only when presented subliminally, have a unique inhibitory effect on conscious symptom targets. This effect is absent when the unconscious conflict primes are presented supraliminally, or when the target is the control words. Unconscious conflict prime effects were found to correlate with a measure of repressiveness in a similar previous study (Shevrin et al., 1992, 1996). Conscious symptom primes have no inhibitory effect when presented subliminally. Inhibitory effects with conscious symptom primes are present, but only when the primes are supraliminal, and they did not correlate with repressiveness in a previous study (Shevrin et al., 1992, 1996). We conclude that while the inhibition following supraliminal conscious symptom primes is due to conscious threat bias, the inhibition following subliminal unconscious conflict primes provides a neurological blueprint for dynamic repression: it is only activated subliminally by an individual's unconscious conflict and has an inhibitory effect specific only to the conscious symptom. These novel findings constitute neuroscientific evidence for the psychoanalytic concepts of unconscious conflict and repression, while extending neuroscience theory and methods into the realm of personal, psychological meaning.

**Keywords: anxiety, defense mechanisms, repression, alpha, EEG/ERP, avoidance, subliminal, neuropsychoanalysis**

## INTRODUCTION

Oddly as psychoanalysis seems to diminish in the eyes of many, neuroscience appears to be taking a long second look at psychoanalysis. Interest and acceptance of an unconscious has been growing. Leading theoreticians have begun grappling with Freud's theory, even thinking of it as the most comprehensive available to psychiatry (Kandel, 1998, 1999), and offering the best account of recent neuroscience findings (Carhart-Harris and Friston, 2010). A growing number of psychoanalysts are going back to Freud's neuroscience roots, finding in his posthumous Project (1950) insightful anticipation of modern neuroscience concepts (Pribram and Gill, 1976). Some have suggested that neuroscience provides the basic science testing ground to avoid the circularity of many psychoanalytic explanations (Rubinstein, 1977). Yet there remain powerful obstacles on both sides to a true fruitful scientific exchange. The neuroscience investigation of the neural correlates of unconscious processes is often limited to automatic biases, ignoring the importance of unconscious conflict, the role of personal meaning, and unique unconscious processes like repression. In contrast, we present the unconscious that is subject to individual meaning (contained in the unconscious conflict unique to each individual), is comprised of complex unconscious emotional processing including repression, and plays a causative role in the manifestation of symptoms as in social phobias. Moreover, we show that these processes are instantiated in identifiable brain events.

Perhaps the two most controversial psychoanalytic clinical concepts are unconscious conflict and repression. On the basis of these two concepts psychoanalysts seek to explain a variety of psychiatric symptoms and how they can be successfully treated. Unconscious conflict is presumed to arise from opposing desires, working largely unconsciously and subject to unconscious efforts at inhibiting or repressing the conflict that can create great anxiety, shape how a person responds to the challenges of life, and can create a variety of psychiatric symptoms such as the social and specific phobias we have investigated.

Yet unconscious conflict theory is not the only theory of psychopathology psychoanalysts espouse. Psychoanalysts often refer

to "conflict theory" as "classical" both in complimentary and pejorative ways. Adherents see it as the original Freudian theory; critics see it as essentially outmoded and replaceable by newer conceptualizations. These different theories all suffer from one fatal flaw-none have achieved the empirical support scientifically required to pass muster as an established scientific theory. Whether you select one theory or another is more a matter of preference than one based on defensible evidence (Rubinstein, 1977). We decided to exercise our preference for conflict theory mainly because it was historically the first and has lasted a considerable time; it was also the one we were best acquainted with by training and clinical experience.

Without doubt one of the most trenchant critics of Freud, Grunbaum (1984) has pointed out that empirical support must come from methods that can be shown to be independent of the clinical method, otherwise circularity is the ever present danger. In response to these challenges, we applied our research method in order to find independent evidence for the validity of the constructs of repression and unconscious conflict. At the same time we believed our research method is theory neutral and could be used by other theories to test their basic hypotheses.

Within psychoanalysis sharply critical voices along the same lines as Dr. Grunbaum have been heard as well. Outstanding theoreticians such as Rapaport (1959) have written extensively on these same issues. It is important to note that Rapaport's influence as a thinker and theoretician went beyond psychoanalysis. He was an early influence on Daniel Kahneman, as Kahneman (2003) noted in his Autobiography. Kahneman's monograph "Attention and Effort" contained a theory of attention as a limited resource to which Rapaport had originally led him (Kahneman, 1973, 2003). Kahneman also incorporated the concept of psychic energy, another important Rapaport theoretical preoccupation and central to Freud's concept of repression that Kahneman found useful and renamed effort (Kahneman, 1973, 2003). Kahneman was intending to spend more time studying with Rapaport; unfortunately Rapaport died prematurely at 50 before Kahneman could pay his return visit. Interactive contacts between psychoanalysts and cognitive and neuroscientists, as between Rapaport and Kahneman, have likely occurred a number of times, but were not sustained or further exploited.

Our research group set about some years ago to venture onto this difficult terrain. The tripartite approach was a natural next step from the senior author's previous research in which he was the first to report event related potential markers of subliminal unconscious processes (Shevrin and Fritzler, 1968), to demonstrate unconscious inhibition (Snodgrass et al., 1993a,b), and to devise methods for investigating two different modes of thought related to Freud's concepts of primary and secondary process: [Shevrin and Luborsky (1961), Brakel et al. (2000), see also Brakel and Shevrin (2003) for a comparison of Freud's theory of primary and secondary processes with more recent cognitive dual process theories].

Our early studies were designed as straightforward cognitive investigations incorporating subliminal and electrophysiological methods. What they all lacked was any clinical data from which the existence of unconscious processes and repression were inferred. The new method sought to correct this lack by including in depth interviews of patients who were also the research participants on whom the inferences derived from the interviews were tested. The initial study we conducted utilizing this tripartite method involved social phobic subjects (described in section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict). A detailed account of the tripartite method and the encouraging findings emerging from this initial study were published in Consciousness and Cognition (Shevrin et al., 1992) and subsequently in a book length treatment including additional findings and three detailed case studies (Shevrin et al., 1996). The main objective of the initial study was to determine that our method would provide objective evidence for the existence of unconscious conflict; secondarily it was hoped that the data would also show a repressive cause and effect relationship between unconscious conflict and conscious symptom experience. This first study (summarized below in section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict) succeeded with its primary objective, but results for the second were ambiguous at best. We realized that we lacked a neural correlate for the nature of the causal relationship between unconscious conflict and conscious symptom experience. A series of subsequent studies (summarized below Previous Studies With Spider Phobia: Alpha Power Serves as an Inhibiting Brain Mechanism in Phobic Experience) were aimed at investigating the role of alpha power as an inhibitory agent that might provide the neural causal link. Following the presentation of these two sets of earlier findings, we describe our new previously unpublished study (section The New Investigation: Establishing a Repressive Causal link Between Unconscious Conflict and Conscious Symptom Experience) replicating and extending these earlier findings, and we believe identifying the neural correlate we were seeking.

## THE INITIAL SOCIAL PHOBIA STUDY: ESTABLISHING CLINICAL AND BRAIN EVIDENCE FOR UNCONSCIOUS CONFLICT

The subjects were eleven social phobics who met DSM IV-R criteria. Four clinician judges selected individual words to be presented as stimuli for each subject. In a within subject design three groups of words were selected. The words were chosen individually for each subject to represent the unconscious conflict, conscious symptom experience, and a group of general negative valence words [see Shevrin et al.(1996, p. 139 Appendix B) for a detailed description of the word selection procedure]. The three word groups were equated for frequency, length, and part of speech (nouns and verbs). All words were presented subliminally and supraliminally. The brain responses were measured by time-frequency features derived from event-related potentials (ERPs). The essential idea behind time-frequency analytic approaches is simple: While standard ERP methods depict brain responses in two dimensions (time and amplitude), time-frequency methods add a third dimension—frequency. Time-frequency methods thus represent event-related brain responses as the frequency and amplitude (more accurately, power) present at each time bin on each trial, rather than only the amplitude at each time bin, as in usual ERP methods. "Time-frequency features," then, refer to points in this three-dimensional space. The application of

time-frequency features was a relatively new approach to ERPs at the time pioneered by co-author Williams (Moser and Avnon, 1986; Williams et al., 1987, 1994; Cohen, 1989; Williams and Jeong, 1989, 1992; Zaveri et al., 1992). See Supplement 1 and Shevrin et al. (1992) for further description.

In this earlier study, we used discriminant analysis to select the t-f features which best differentiated the critical unconscious conflict and conscious symptom word stimulus categories (vs. general negative words). These disciminant analysis/classification findings were then internally cross-validated by performing a standard development vs. test set (i.e., odd vs. even-numbered trials) analysis. The t-f feature analysis and its use are explained in the book length presentation (Shevrin et al. 1996, p. 139 Appendix B).

The main finding was a significant two way interaction between word category (unconscious conflict vs. conscious symptom) and duration (subliminal vs. supraliminal). The brain responses to the unconscious conflict words were more correctly classified subliminally as compared to the general negative valence control; the reverse was found for the brain responses of the conscious symptom words (Shevrin et al., 1992, 1996). A second finding concerned repressiveness as measured by a Hysteroid-Obsessoid Questionnaire (HOQ) that the subjects completed. The HOQ is a self-report personality trait instrument originally developed to measure obsessive vs. hysterical personality styles (Caine and Hawkins, 1963; Caine and Hope, 1967). Psychoanalytic theory suggests repressive defenses should be prominent in those with the latter style. Further, earlier work (Ludolph, 1981; Shevrin et al., 2002a) found significant positive relationships between hysterical/repressive HOQ scores and various other indicators of repressive defenses (e.g., related indexes on the Rorschach). These two tests arrive at measures through largely different methods. Here, in the initial social phobic study, the HOQ predicted better classification of UC stimuli subliminally, but poorer classification of UC stimuli supraliminally. This finding suggested that an inhibitory repressive process was at work when the unconscious conflict words were presented supraliminally, inhibiting conscious recognition of their unconscious significance. The comparable correlations for the conscious symptom words and the control words were both non-significant (Shevrin et al., 1992, 1996). These two findings, inferred from clinical material by subjective clinical judgments, and hypothesized to be a cause of the symptom, were paralleled by objective time-frequency measures of unconscious processes.

The conflict stimuli selected were unique for each subject, a practice rare in cognitive research. Nevertheless, the positive results demonstrated that these different stimuli across subjects produced similar results (Shevrin et al., 1992, 1996). We further tested whether the unconscious conflict and conscious symptom words formed unique categories by scrambling the words across categories to form new pseudo-categories. We used an information flow measure (Kushwaha et al., 1992), an adaptation of Shannon-type information measures, to assess stimulus-related information flow between pairs of electrodes. Although this measure cannot tell us what aspects of the ERP response (e.g., amplitude, frequency, etc.) are carrying this information, it does—critically—measure specifically stimulus category-related information (vs., e.g., other information flow analytic techniques which do not distinguish category-related vs. background activity). See Supplement 1 of the current manuscript for further explanation the information flow technique, and Kushwaha et al. (1992) for full details. Substantively, Kushwaha et al. found that significantly more stimulus related information flowed between electrodes for the true categories than for the pseudo-categories, convergently indicating that the former were indeed true categories. Additionally, we found greater information flow when the unconscious conflict words were presented subliminally as compared to supraliminally (Kushwaha et al., 1992).

The evidence from the first study with social phobics established the existence of unconscious conflict on the basis of clinical and independent non-clinical methods. It seemed clear that the unconscious conflict stimuli formed unique, individually meaningful categories. However, what was not clear is how these stimuli acted as causes of conscious symptom experience.

## PREVIOUS STUDIES WITH SPIDER PHOBIA: ALPHA POWER SERVES AS AN INHIBITING BRAIN MECHANISM IN PHOBIC EXPERIENCE

We then set about to investigate the link between unconscious conflict and conscious symptom experience. In our subsequent studies, we shifted our primary measure of physiological brain activity from time-frequency features to alpha power measures. We did so because much recent evidence had suggested that alpha power may be an important brain mechanism for inhibiting task irrelevant stimuli. For example, if the same frequency light was presented to each eye and the subject was instructed to pay attention only to the left eye, alpha power contralateral to the right eye increased significantly. Alpha power played a role in inhibiting attention to the right eye (Kelly et al., 2006). If this inhibitory function were generalizable it might provide the inhibitory function involved in repression. Charles Brenner, a leading psychoanalytic theoretician, had earlier hypothesized that psychodynamic defenses like repression were made up of normal cognitive functions that were put to specific unconscious motivational uses (Arlow and Brenner, 1964; Brenner, 1976, 1982). It would follow from this hypothesis that alpha power might provide the inhibitory function needed for repression, while the motivation for the inhibition would derive from the person's unconscious conflict. If so then alpha power might be the means by which to quantitatively measure the causal inhibitory link between unconscious conflict and conscious symptom experience.

We set about conducting a series of experiments with spider phobics. We presented phobic spider images and controls, subliminally and supraliminally. An FFT measured alpha power in the 8–13 frequency range. Subjects also completed a standard detection procedure with subliminal images, and rated their fear of spiders before and after the subliminal presentations (Shevrin et al., 2010; see Supplement 2 for the published poster abstract). Snake phobics served as a control for phobic state and rectangles served as a neutral stimulus control. In this study with spider phobics we did not assess unconscious conflict; our limited aim was to see if for spider phobics alpha power inhibited responses to spider stimuli and other spider related responses. If this turned out to be the case, then the inhibiting function of alpha power could

be generalized beyond the purely cognitive inhibition of distracting or irrelevant stimuli to inhibiting relevant but emotionally disturbing stimuli. It might then approximate, from a psychoanalytic standpoint, a defense resembling repression once it could be linked to a related unconscious conflict.

The results were encouraging. Increased alpha power correlated with: (1) diminished attention to the phobic spider stimulus as reflected in smaller N100 amplitude and delayed N100 latency, (2) below chance (inhibited) detection of spider stimuli in a standard detection procedure, (3) greater self-reported levels of spider fear, (4) worsening spider fear after repeated subliminal exposure. Control results for snake phobics and rectangles for these comparisons were all non-significant (Shevrin et al., 2010; see Supplement 2 for the published poster abstract).

The results from this study with spider phobics demonstrated that alpha power went far beyond inhibiting attention to purely cognitively irrelevant stimuli. Rather, alpha power played an inhibitory role: (1) when the perceptual stimulus was emotionally significant (a feared spider), (2) when the task was to attend to an emotionally significant stimulus, (3) when the phobic stimulus elicited greater anxiety and fear, and (4) when multiple subliminal exposures did not decrease phobic spider fear. The finding that avoidance worked against improvement following multiple subliminal presentations of spiders suggested that the research might have treatment implications (Shevrin et al., 2010). It was as if the inhibitory process was flexible and not bound to a particular task. Rather, it served a specific unconscious motivation that could be imagined in these words, "I am afraid of spiders and I don't want to have anything to do with them. I will inhibit any process that increases the likelihood of exposure to spiders." When put in these terms it begins to sound like repression. Indeed, as cited previously, Brenner defined defenses from a psychoanalytic standpoint as a particular cognitive function linked to a particular motive. In this instance the particular cognitive function was inhibition associated with alpha power, and the motive was to avoid or minimize fear or anxiety with respect to spiders. These strong indications that alpha power may serve as the inhibitory brain mechanism of repression lead us to focus on the role of alpha power in the new, original study to be reported below.

## THE NEW INVESTIGATION: ESTABLISHING A REPRESSIVE CAUSAL LINK BETWEEN UNCONSCIOUS CONFLICT AND CONSCIOUS SYMPTOM EXPERIENCE

Much cognitive research had long called attention to the central role of avoidance in anxiety disorders. In our research we sought to demonstrate that avoidance was related to unconscious conflict and repression, and generalizable across many different tasks. Moreover, these processes could all go on unconsciously. It is notable that recently, Klimesch et al. (2011) have provided extensive cognitive neuroscience evidence that alpha power serves a general inhibitory function not limited, as heretofore believed, to distracting and irrelevant stimuli. Its inhibitory function can be applied to different tasks and stimuli determined by a variety of top down influences such as expectations. These considerations parallel our own conclusions reported in Shevrin et al. (2010).

In our first social phobia study (section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict) we showed that unconscious conflict based on in-depth clinical data exists, but we could not claim that the evidence established a causal link between unconscious conflict and conscious symptom experience. In the spider phobia study (section Previous Studies With Spider Phobia: Alpha Power Serves as an Inhibiting Brain Mechanism in Phobic Experience; Shevrin et al., 2010) we showed how alpha power functioned to inhibit responses to a subliminal phobic stimulus on different tasks (e.g., attention, detection, etc.). From a psychoanalytic standpoint, the important missing piece in the spider phobic study was the underlying unconscious conflict creating the necessary motivation for inhibition or repression of spider stimuli. It seemed clear that now we needed to show that alpha power served as the causal neural link between unconscious conflict and clinically based conscious symptom experience.

According to psychoanalytic conflict theory (Freud, 1955, 1957, 1959; Brenner, 1982), neurotic disturbances are the consequence of a conflict of motives operating largely unconsciously. Any effort to investigate this proposition must: (1) infer from appropriate clinical material that a particular conflict causes a specific neurotic disturbance, (2) demonstrate that only when the conflict is activated via subliminal presentation (so that it is active outside of the person's awareness) does it produce an inhibitory response in the conscious neurotic disturbance, (3) show that when the unconscious conflict stimuli are supraliminal (so that they are processed consciously) they will not produce these inhibitory effects specific to the conscious neurotic disturbance, (4) ascertain that when control conscious experiences other than the specific neurotic disturbance are involved there will be no evidence of an unconscious conflict inhibitory effect either subliminally or supraliminally. To summarize: The relevant unconscious conflict specific to the neurotic disturbance has its inhibitory effect on the neurotic disturbance only when the unconscious conflict is activated subliminally, and only with respect to that neurotic disturbance (i.e., the conscious symptom stimuli). In short, the inhibition is unconscious and specific to the particular neurotic disturbance.

But why should the inhibitory repressive process triggered by the activation of unconscious conflict also lead to inhibition related to the conscious symptom experience? In the current experiment, the critical condition involves initially subliminally presenting words related to participants' unconscious conflict, rapidly followed by words related to their conscious symptom experience. These conscious symptom words describe the aspects of the social situation that are most anxiety provoking and fearful to the participant, as well as the physiological signs of anxiety the participant experiences in the uncomfortable social situation. In effect, the presentation of these words places the participant consciously into the dreaded socially feared situation. But—and this is critical—these social situations are dreaded precisely because they themselves also resemble the participant's unconscious conflict. If they did not, participants would not exhibit symptoms in response to such situations. This fact highlights a fundamental point—that conscious symptoms (taken together with the situations that trigger them) are related to and interconnected with the underlying unconscious conflict. The participant experiences social situations as if they contain an aspect of the

unconscious conflict, although the participant does not realize that their unconscious conflict is influencing their conscious experience. For example, if the participant's unconscious conflict revolved around his relationship with his father (as suggested by example in Supplement 3), then the participant will experience certain social interactions in the same framework as he experienced his conflictual interactions with the father. Consciously, it becomes a struggle between enjoying the social occasion and tolerating increasing anxiety generated by its unconscious significance. Thus, from a psychodynamic perspective, repression must be directed from the activated unconscious conflict toward the social situation, or the most (unconsciously) conflictual aspects of it. Accordingly, attempts to inhibit and repress activation of the unconscious conflict should predict attempts to inhibit and repress responses to the conscious symptom stimuli. Therefore, we would expect to find a positive correlation between inhibition of unconscious conflict, and inhibition of the following conscious symptom reminders. By contrast, purely cognitive accounts, which lack any concept of unconscious conflict, would predict no relationship at all between the two kinds of stimuli.

The novel methodological innovation in this new study was to show that inferences drawn from entirely qualitative psychoanalytic clinical material can be tested by objectively measurable brain processes so that what is ultimately demonstrated is an underlying commonality of function between psychodynamic and brain processes.

The major change from the original experimental design of the first social phobia study was to shift to a priming model in which the unconscious conflict stimuli preceded the conscious symptom stimuli. A priming model allowed us to empirically assess the effects of the unconscious conflict stimuli on the following conscious symptom stimuli, and to scrupulously control for any potential confounding influences. In all other respects the design of this new study, presented in detail below, was exactly the same as of our first study, described in Shevrin et al. (1992).

## METHODS AND MATERIALS

### PARTICIPANTS

Ten subjects (7 women, 3 men) who met DSM IV-R criteria for social phobia were selected. The subjects provided written informed consent prior to participation in the study. The study was approved by the University of Michigan Medical School Institutional Review Board (IRBMED) Ethics Committee.

### PROCEDURE

After the participants had been selected, 3–4 hour taped diagnostic interviews were obtained from each participant and transcribed for examination and word selection [see Shevrin et al. (1996, 59–90) for details; Chapters 9, 10, 11 for detailed case studies]. This procedure yielded the Unconscious Conflict (UC) and Conscious Symptom (CS) primes, selected individually for each participant. Conscious Symptom (CS) word targets were also drawn from these interviews, and when such words appeared both as primes and targets they were always non-identical. A set of Osgood Negative Valence (ON) words, selected uniquely for each participant, served as the control (Osgood et al., 1975). For each of the word groups (UC, CS, and ON) judges selected seven words for each participant. The three word groups were equated for frequency, length, and part of speech (nouns and verbs). In Supplement 3, we present a sample set of words for each of the three categories of stimuli for one subject.

The selected words were presented tachistoscopically to the participants. The key experimental condition was subliminal unconscious conflict primes followed by supraliminal conscious symptom targets. This critical condition was embedded in a Prime Type (unconscious conflict vs. conscious symptom) × Target Type (conscious symptom vs. Osgood negative valence) × Prime Duration (subliminal vs. supraliminal) 2 × 2× 2 within-participants factorial design. Every presentation consisted of two words, the prime and the target, presented 1000 ms apart. All primes were presented subliminally as well as supraliminally, whereas the targets were always supraliminal. Each prime word was paired with every target word for a total of 196 subliminal and 196 supraliminal trials (e.g., unconscious word prime 1 was paired with all 14 CS and ON targets). All subliminal prime trials were presented first, followed by all supraliminal trials. Otherwise, prime–target pairs were randomized. Participants were simply instructed that at a prearranged signal they should fixate on a dot in the center of a blank field and not blink or move their eyes until signaled that the trial was complete.

The subliminal stimuli were presented for 1 ms duration, 10 ft/lamb.; supraliminal duration was set at 30 ms, 10 ft/lamb. These durations are much briefer than in typical subliminal studies. We used a Gerbrand Model 3-field Dodge-type tachistoscope, which is capable of much faster durations than a computer that requires backward masking to achieve subliminal presentations. Ambient light was set at 10 ft./lamb., matching the luminance of the stimuli [see Shevrin et al. (1996) for successful application of these settings].

### MEASURES

EEGs were recorded from 10 electrodes (SCR, OB muscle, Corrugator muscle, F3, F4, CzPz, P3, P4, Oz, EOG) with reference to linked ears (A1 + A2). A 10–20 electrode placement system was used for application of electrodes. Silver-silver chloride electrodes were used with impedance kept below 5 K Ohms. Originally data was collected at 500 samples per second and then down sampled to half at 250 samples per second for 2 s and 400 ms. A total of 600 bins or 2400 ms of data were collected. Grass model 8 EEG machine was used to amplify EEGs and a hardware filter of 0.3–125 Hz was used. LabView on a Macintosh computer was used to digitize EEGs. Digitized data were then transferred to a LINUX PC for further analysis. MATLAB was used for doing FFT and Alpha band power calculations. Alpha power (8–13 Hz), calculated via the Fourier transform, was determined for the subliminal and supraliminal prime (1000 ms) and target (1000 ms) epochs post-stimulus for each trial, and then averaged within-condition (e.g., subliminal UC primes when followed by CS targets, etc.). For each participant there were a total of 49 trials averaged for each prime and target category. The experimenter visually inspected EEG recordings online for artifacts resulting from eye movement, muscle movement and 60 Hz. Trials containing such artifacts were rejected online. The stimuli were then repeated in the next trial and EEG data

was re-recorded. Because we did not initiate trials until participants indicated their readiness and the ongoing EEG was artifact-free, very few trials (1–3%) needed to be repeated, and the proportions of such trials did not differ between conditions. Because the alpha power distribution was notably skewed across participants, alpha power was log-transformed before further analysis.

The measure of alpha power we used was absolute alpha power. We did not divide prime or target alpha by a baseline so the units in the figures simply reflect alpha power for both the *x*- and *y*-axes. While some researchers divide post-stimulus alpha by a preceding baseline, others often simply analyze unmodified post-stimulus alpha power. Both methods are equally valid. For example, Cooper et al. (2003) and Kelly et al. (2006), cited as prior research for our own, found increases in absolute alpha power to play inhibitory roles.

### DATA ANALYSIS

Our main interest was in examining the influence of prime alpha power on target alpha power. To this end, we analyzed prime influences using a regression approach in which alpha power for the two primes (UC and CS) were predictors, and target alpha power was the dependent (criterion) variable. The regression approach allows estimation and comparison of the unique (i.e., uncorrelated) abilities of the two prime types to predict target alpha. In contrast, in the more commonly used difference score approach (e.g., UC—CS primes) to examining prime-target relationships, it is not possible to examine the contributions of the UC vs. CS primes independently, thus leaving it ambiguous as to which of the two factors caused a positive result. Although not presented here, the main difference results from these data largely converged with the regression results presented below.

One might also maintain that the main analysis, rather than regression, should have been a comparison of mean effects in an ANOVA. In many situations analyzing the means is helpful. Here, however, such analyses are of secondary interest, because we are critically interested in the *relationship* between prime and target alpha (i.e., the predictive/causal relationships between the two). Further, correlations as in regressions are independent of means and mean differences. For example, mean 1 could be larger than mean 2, but this says nothing about whether scores in condition 1 are correlated with scores in condition 2. We have previously documented in our review (Snodgrass et al., 2004a), extremely subliminal conditions (i.e., wherein detection $d' = 0$) frequently yield exclusively *bidirectional* effects—that is, effects driven by individual differences but with no main (i.e., mean) effects. This is exactly the case with our data: An ANOVA on our data produced no mean effects, while the regression analysis was strikingly productive. For a comprehensive report of the data, we present means for all prime and target categories, as well as an ANOVA analysis in Supplement 4.

Because the subliminal vs. supraliminal prime duration manipulation is of great interest, we wished to analyze these conditions separately, so that any differences between subliminal vs. supraliminal effects would emerge. Regarding reporting R-square, often cited in regression analyses, in our case this would be uninformative or even confusing, for several reasons. First, we are only interested in possible differences in effects associated with UC vs. CS prime types (i.e., in regression language, their unique contributions to predicting target alpha). Such differences are captured precisely by the (unique) partial correlations currently reported in the text. In contrast, overall R-square reflects not only the predictors' unique contributions, but also any predictive contribution made by the predictors' shared (common) variance—and this variance is not of interest here. The current focus on unique prime type contributions to predicting target alpha removes these uninformative effects.

Our core hypothesis was that the degree of alpha power-related (i.e., inhibitory/repressive) brain activity in the UC primes should predict increased alpha power in the CS targets (i.e., signaling increased inhibition/avoidance), but not for unrelated ON targets. In keeping with our prior results from the first social phobic study (section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict; Shevrin et al., 1992, 1996), this effect should manifest with UC subliminal but not UC supraliminal primes. In parallel fashion, any CS prime influences on CS or ON targets should manifest more strongly supraliminally than subliminally, an expectation based on the first social phobic study in which CS effects were only supraliminal (section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict; Shevrin et al., 1992, 1996).

## RESULTS

Four separate regressions were performed: (1) Subliminal primes (UC, CS) with CS target; (2) Supraliminal primes (UC, CS) with CS target; (3) Subliminal primes (UC, CS) with ON target; and (4) Supraliminal primes (UC, CS) with ON target. We began by averaging across all six electrodes (F3, F4, CzPz, P3, P4, Oz).

### UNCONSCIOUS CONFLICT PRIMES (UC): SUBLIMINAL AND SUPRALIMINAL RESULTS

Subliminal UC prime alpha as hypothesized positively predicted CS target alpha, [$t_{(7)} = 2.47$, $p = 0.043$, $\beta = 1.08$, partial $r = 0.68$]. (The scatter plot showing this central hypothesized relationship is presented in **Figure 1**.) By contrast, subliminal UC prime alpha had no effect on ON control target alpha [$t_{(7)} = 0.79$, $p = 0.45$, $\beta = 0.36$, partial $r = 0.29$]. (The scatter showing an absence of an effect for this control condition is presented in **Figure 3**). When UC primes were supraliminal they no longer predicted CS target alpha: [$t_{(7)} = 0.74$, $p = 0.49$, $\beta = 0.28$, partial $r = 0.27$], and had no effect on control ON targets [$t_{(7)} = -0.81$, $p = 0.45$, $\beta = -0.44$, partial $r = -0.29$]. Thus, only when the UC primes were subliminal, and only when they preceded the CS targets did they produce an enhanced alpha effect.

### CONSCIOUS SYMPTOM PRIMES (CS): SUBLIMINAL AND SUPRALIMINAL RESULTS

Subliminal CS primes, unlike subliminal UC primes, did not predict CS symptom alpha [$t_{(7)} = -0.21$, $p = 0.84$, $\beta = -0.09$, partial $r = -0.08$]. (The lack of a relationship in this control condition is shown in the scatter plot in **Figure 2**.) The subliminal CS primes also did not predict control ON target alpha

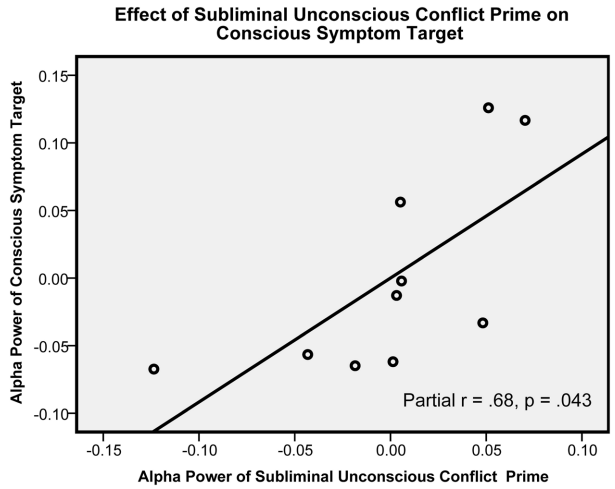


**FIGURE 1 | This figure shows the key hypothesized relationship (partial r) between subliminal unconscious conflict prime alpha and the following conscious symptom target alpha.** Alpha power units are in squared microvolts, log-transformed. This graph includes measures averaged across all electrodes.

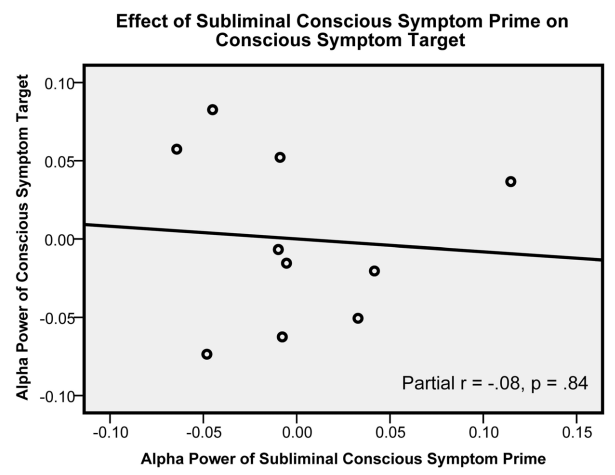


**FIGURE 2 | This figure shows a control condition, in which the relationship present in Figure 1 disappears.** In this figure, subliminal conscious symptom primes were presented (instead of the subliminal unconscious conflict primes in **Figure 1**). The graph shows the partial *r* between subliminal conscious symptoms prime alpha and conscious symptoms target alpha. Alpha power units are in squared microvolts, log-transformed. This graph includes measures averaged across all electrodes.

$[t_{(7)} = 1.38, p = 0.21, \beta = 0.63$, partial $r = 0.46]$. Supraliminal CS primes came close to positively predicting CS target alpha: $[t_{(7)} = 1.81, p = 0.11, \beta = 0.70$, partial $r = 0.56]$, and did positively predict ON target alpha $[t_{(7)} = 2.62, p = 0.034, \beta = 1.42$, partial $r = 0.70]$. Finally, given the similar results for supraliminal CS primes with both CS and ON targets, we also pooled both targets, yielding an overall near-significant result; $[t_{(7)} = 2.15, p = 0.069, \beta = 1.11$, partial $r = 0.63]$.

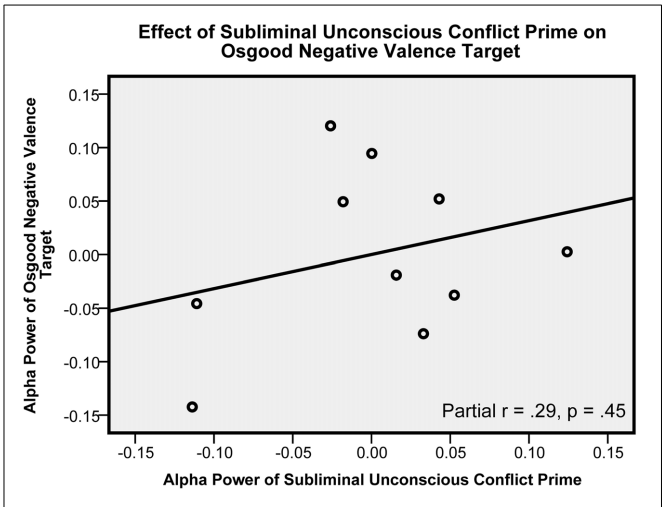


**FIGURE 3 | This figure shows that the relationship presented in Figure 1 is absent in another control condition.** Here, the conscious symptoms targets (as presented in **Figure 1**) are replaced with the control Osgood negative valence target. The graph shows the partial *r* between subliminal unconscious conflict prime alpha and Osgood negative valence target alpha. Alpha power units are in squared microvolts, log-transformed. This graph includes measures averaged across all electrodes.

### *POST-HOC* FINDINGS

Upon examining parallel analyses for individual electrodes, we noticed an apparent frontal (F3, F4, CzPz) vs. parietal (P3, P4, Oz) pattern. We then averaged across these electrode subgroups. For economy of exposition we focus on the main results; other findings never approached significance and showed no frontal vs. parietal differences. These analyses suggested that the critical subliminal UC/CS finding was strongly present parietally: UC prime alpha $[t_{(7)} = 3.95, p = 0.006, \beta = 1.37$, partial $r = 0.81]$, but non-significant frontally: UC prime alpha $[t_{(7)} = 1.16, p = 0.28, \beta = 0.57$, partial $r = 0.40]$. Conversely, the supraliminal CS prime findings were stronger frontally [CS target: $t_{(7)} = 2.33$, $p = 0.05, \beta = 0.65$, partial $r = 0.66$; ON target: $t_{(7)} = 3.67, p = 0.008, \beta = 1.27$, partial $r = 0.81]$, but non-significant parietally [CS target: $t_{(7)} = 1.43, p = 0.20, \beta = 0.69$, partial $r = 0.48$; ON target: $t_{(7)} = 1.27, p = 0.24, \beta = 1.01$, partial $r = 0.43]$. Again we note the inverse reciprocal relationships between unconscious conflict and conscious symptom results as a function of category and duration, paralleling findings from the first social phobic study (Shevrin et al., 1992, 1996).

### BOOTSTRAP APPROACH REGRESSIONS

While the above findings confirmed our key hypotheses, one might worry that regression methods with small samples such as ours could yield unreliable results. Bootstrap methods, which repeatedly reanalyze the sample data using random resamples, are a useful tool to check this concern because they non-parametrically estimate the sampling distribution using the actual sample data rather than relying on standard assumptions (Fox, 2008). Here, we reran our primary regression analyses, now incorporating related bootstrapping techniques. For all electrodes combined, the critical subliminal UC prime/CS target effect actually improved slightly ($p = 0.018$), while the subliminal CS

prime/CS target effect remained non-significant ($p = 0.79$), as did both UC prime controls (subliminal UC prime/ON target, supraliminal UC prime/CS target), $ps > 0.35$. Further, the relevant univariate distributions and regression diagnostics indicated no outliers with these key effects, suggesting these findings were not distorted by this potential problem. Finally, the non-predicted supra CS prime/CS target and supra CS prime/ON target effects also improved slightly ($ps = 0.084$ and 0.009, respectively). Overall, then, applying bootstrapping to the critical effects suggested they were reasonably stable.

## DISCUSSION

The pattern of results supported our main hypothesis for unconscious conflict. Only when the unconscious conflict primes were subliminal did they significantly predict conscious symptom target alpha power. The alpha effect was not present: (1) when the unconscious conflict primes were supraliminal, (2) when the conscious symptom stimuli were the subliminal primes (3) when the control Osgood Negative words were the supraliminal target stimuli. In short, there was only one condition in which the unconscious conflict primes were associated with enhanced alpha power: when the subliminal unconscious conflict primes were followed by supraliminal conscious symptom targets.

These findings strengthen the interpretation of a cause and effect relationship between unconscious conflict and conscious symptom experience. Of particular importance to supporting our hypotheses, we did not simply obtain some single, isolated finding consistent with this hypothesis. Rather, based on coherent, interrelated psychoanalytic theory relevant to our hypothesis, we predicted—and obtained—an interrelated *pattern* of findings, including not only specifying where we *should* obtain the predicted result (i.e., with subliminal UC primes and CS targets), but also where we *should not* obtain the result (i.e., with ON targets or with supraliminal UC primes). Notably, we obtained this entire pattern, strengthening the likelihood that the key results are genuine—and meeting specific recommendations by Grunbaum regarding testing this fundamental psychoanalytic causal hypothesis.

The one seemingly anomalous finding, not in itself central to our hypotheses, was the alpha power effect found for the supraliminal CS primes and the ON target alpha power. Since these results were not predicted, they may possibly represent a false positive finding. Nevertheless, one might wonder that if any inhibitory effects can occur with CS primes whether that challenges the specificity of the relationship between UC primes and repression. We deal in some detail with this troublesome issue below, calling attention in particular to the findings that CS prime inhibition never occurs subliminally, it is not correlated with repression in the initial social phobia study, and it does not cleanly discriminate between conscious symptom experience and the ON control targets [the near significant conscious symptom result ($p = 0.11$)], suggesting that the inhibition is directed at negative valence words rather than specifically directed at the CS primes.

From this pattern of converging experimental and control results we are in a position to infer that only the unconscious conflict stimuli selected *a priori* by psychoanalysts from clinical data *causally link clinical inferences based on psychological meaning (unconscious conflict over emotionally incompatible desires) with brain processes (patterns of electrophysiological inhibition)*. If so, then to our knowledge this is the first *psychophysiological* evidence for Freud's unconscious conflict theory of psychopathology. Repression emerges as a function of these inhibitory patterns, as it does in the patterns of psychological avoidance and choice. From this standpoint, repression is not a neural or psychological "force," but a series of unconscious decisions creating a pattern of interactions with oneself and the world. That was what we found with the pattern of interactions for the unconscious conflict primes in the current study in which inhibition occurs subliminally, but not supraliminally.

Could alternative cognitive explanations account for some of the effects described in our results? The simple answer is that semantic priming would not predict any relationship at all between the unconscious conflict primes and the conscious symptom targets because the unconscious conflict primes do not constitute a semantic category at all, let alone one with any relation to the conscious symptom category. Indeed, as mentioned in the text, the participants in our earlier social phobia study themselves did not regard the unconscious conflict primes as a category when asked to consciously categorize the stimuli post-experimentally. On the other hand semantic priming accounts could explain the results involving the conscious symptom primes and conscious symptom targets, as these do constitute standard "related" categories. This is perfectly fine with us; we never thought such accounts would not apply to purely conscious symptom-related effects. Similar reasoning applies to emotion-attention accounts; like semantic priming, they would predict no relationship between UC primes and CS targets (because the UC primes do not comprise a standard emotional category), but could account for relationships between CS primes and CS targets (which do). Furthermore, attentional blink phenomena require much shorter prime-target SOAs (c. 200–300 ms) than ours (c. 1000 ms), so this mechanism could not account for our results.

What is it that needs to be explained and further understood about the phobic experience and how would our findings based on psychoanalytic concepts advance that understanding? It is clear that the phobic experience is one of fear, anxiety, avoidance, at times revulsion and disgust. Most important is the general observation that the phobic person is aware that these reactions are not substantiated by the nature of the actual phobic object or situation. Moreover, there is no agreed upon explanation on how a phobia develops or is sustained. For the psychoanalyst there might be an answer to be found to these questions when the role of unconscious conflict is taken into account. Perhaps surprisingly, we learn that it is not the phobic object or situation taken in its literal significance that is the source of the phobic experience amply reflected in the conscious symptom accounts. Instead, it is the way these accounts are related in significance to unconscious conflict, so that the conscious symptom experience falls prey to the same repressive influences as are present in the unconscious conflict and are reflected in our key findings. The conscious phobic experience is transformed into a stage on which invisible actors reenact the unconscious conflict scenario, out of keeping with what is happening visibly. Thus, the repression triggered by the activation of the unconscious conflict, should in a

similar manner be directed toward the conscious symptom experience. Our results support this understanding with new evidence drawing on brain based inhibitory processes, as well as clinically based accounts of unconscious conflict. However, the influence of unconscious conflict on conscious symptom formation, and the role of repression and inhibition in this process presents a complex system which may unfold differently in different situations, such as different psychopathology or different experimental measures. The exact mechanism of this complex relationship is for future research to determine. But our findings tell us that, beyond the immediate largely conscious avoidant reactions, there are important new parameters to be take into account, namely unconscious conflict and repression.

Two findings require further examination: (1) for the unconscious conflict primes to have an alpha power effect on the conscious symptom experience they must first be subliminal, (2) whereas the conscious symptom primes exercise alpha power effects only supraliminally.

### THE SUBLIMINAL CONDITION AND ALPHA POWER EFFECTS AT THE OBJECTIVE DETECTION THRESHOLD (ODT)

At the beginning of the senior author's program of research on unconscious processes, he decided to present stimuli at the fastest duration possible with equipment available at the time. The tachistoscope was the equipment of choice because it could deliver reliably (checked by oscilloscope) a 1ms duration at moderate luminance (10 ft/candles). Under these conditions stimulus detection was at chance (50%). In a series of studies (Shevrin, 1973) replicable subliminal effects were obtained under these conditions.

Snodgrass in a series of subsequent studies (Snodgrass et al., 1993a,b, 2004a,b) combined a signal detection theory approach with Shevrin's earlier psychophysical method, making it possible to go beyond the limitations of classical psychophysics and assess accuracy separately from bias. This made it possible to obtain an accurate measure of the objective detection threshold (ODT) free of criterion bias at which detection ($d'$) was not different from zero. Subsequent research revealed that at the ODT different things happen than at the supraliminal threshold. For example, in a series of replicated studies (Snodgrass et al., 1993a,b, 2004a,b), Snodgrass discovered inhibitory processes at the ODT that were a function of individual differences, findings quite germane to our current study. These effects were based on standard cognitive tasks (e.g., word choices). At the ODT different kinds of thought processes might be occurring. This was borne out in another study on language processing in which palindrome, or reverse word priming, was found at the ODT, but not in the supraliminal condition where only standard forward priming occurred (Villa et al., 2006a,b). The ODT may not only be the purest unconscious state our current methods can produce, but may also constitute a qualitatively different psychophysiological state susceptible to unconscious conflict activation. (It is also possible that similar findings might occur at other subliminal thresholds such as the subjective threshold at which $d' > 0$, but participants aver that they do not see the stimulus, hence subjective (Snodgrass et al., 2004a,b). This remains for future research to determine). These ODT findings raise the possibility that when the unconscious conflict primes are processed at the ODT they become sensitive to individual differences, among them, the inhibitory and repressive processes we have found that do not happen when the same words are processed supraliminally.

### THE SUPRALIMINAL CONDITION AND THE CONSCIOUS SYMPTOM EXPERIENCE

If the reasoning offered above for the unconscious conflict primes at the ODT is correct, why doesn't it also work for the conscious symptom primes when they are subliminal, but appear to work only when they are supraliminal? Here two findings from the initial social phobic study (section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict) are pertinent. First, the repressiveness personality measure predicted t-f subliminal vs. supraliminal classification for the unconscious conflict primes only. This relationship was not found for the conscious symptom stimuli. Moreover, supraliminally the unconscious conflict primes were not significantly grouped together either by the t-f feature analysis or by participants' own category groupings. They simply did not form a category supraliminally (Shevrin et al., 1992, 1996). This was further confirmed by Kushwaha et al.'s (1992) information flow analyses, which showed that the unconscious conflict category showed more information flow subliminally than supraliminally, and more than control pseudo-category analyses. Thus, the unconscious conflict primes were a meaningful category only subliminally in the first study (section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict), and it was only this category that had a significant subliminal alpha power inhibitory effect on the supraliminal conscious symptom targets, in the new, or second social phobic study (section The New Investigation: Establishing a Repressive Causal Link Between Unconscious Conflict and Conscious Symptom Experience). By contrast, participants in the initial study (section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict) had no difficulty in treating the supraliminal conscious symptom primes as a category expressing what the participant had previously described as disturbing about the phobic experience. None of this could be said about the supraliminal unconscious conflict primes (Shevrin et al., 1992, 1996).

On these grounds it seems reasonable to suppose that the supraliminal conscious symptom words were overtly disturbing to the participants because they brought back the conscious social phobic experience itself. And when at the same time participants in the second study (section The New Investigation: Establishing a Repressive Causal Link Between Unconscious Conflict and Conscious Symptom Experience) were exposed supraliminally to other quite negative stimuli (other conscious symptom words or Osgood Negative words), participants would be disposed to respond with efforts at inhibition or avoidance, now completely conscious.

When we compare the *supraliminal conscious symptom prime condition* with the *subliminal unconscious conflict prime condition*, in both of which evidence for inhibition appears, differences are found that inform us of the difference between conscious and unconscious inhibition. For example, there is no evidence that the

inhibition following the supraliminal conscious symptom prime condition has any of the characteristics of repression. In contrast, multiple sources of evidence point to an association between the subliminal unconscious conflict prime condition and repression. The unconscious conflict prime condition showed a relationship to the repression personality measure in the first study (section The Initial Social Phobia Study: Establishing Clinical and Brain Evidence for Unconscious Conflict; cf. Shevrin et al., 1992, 1996), as well as to an independent projective behavioral measure of repression, with both of these indexes of repression being highly correlated (Caine and Hawkins, 1963; Caine and Hope, 1967; Ludolph, 1981; Shevrin et al., 2002a,b). But at the heart of the matter is the second study's central finding that only the subliminal unconscious conflict primes activate the unconscious conflict; while the supraliminal conscious symptom prime condition activates the conscious phobic experience. This difference between what the participant is aware of fearing consciously and seeks to avoid consciously and what constitutes repressed unconscious knowledge related to these conscious fears lies at the heart of the psychoanalytic conception of psychopathology.

## LIMITATIONS

Although a substantial amount of prior work (cited above) supports the inhibition interpretation that we provide for alpha power, some (e.g., Palva and Palva, 2007) have suggested other functions of alpha. However, we note their position is based on phase-locked alpha, not non-phase-locked alpha as in our research and in the alpha/inhibition literature generally (e.g., Kelly et al., 2006). Also, Palva and Palva's alternative interpretation is specifically linked to supraliminal stimuli (see their p. 157, box), and is hence likely not applicable here in any case.

It also might have been useful to have here included a behavioral measure as an independent indicator of inhibition. We note, however, that our previous spider phobia study (Shevrin et al., 2010) suggested that greater alpha power was indeed associated with inhibited performance on a behavioral signal detection task. Nonetheless, our and others' future work would benefit from routinely including behavioral measures of inhibition. We also note that our stimulus materials (especially UC words), while balanced on many factors (frequency, length etc.), could not be balanced for all possibly relevant dimensions (e.g., arousal). This is a necessary limitation due to their completely individualized nature, a unique feature of this study perhaps essential to investigating the impact of intrinsically idiographic UC (and to a lesser extent, CS) stimuli—a fundamental goal of the current line of research.

Finally, our sample size is small, which raises potential statistical bias/instability issues with regression approaches such as ours. The bootstrap analyses, however, suggested our regression results were reasonably stable, and there was no indication of potentially distorting outliers. Nonetheless, because this is a small-sample single study, further replication with larger samples is needed to more firmly establish our conclusions. We plan such a larger-scale replication, which would additionally include other valuable data-analytic approaches such as single-trial analyses and robust regression methods, as well as a behavioral measure of inhibition.

## FUTURE DIRECTIONS

One future direction would take us to applied clinical research. We would expect that following successful psychodynamic, conflict oriented treatment, the same unconscious conflict prime words presented after treatment would no longer have an enhanced inhibitory effect on conscious symptom targets. It would no longer be needed. Another direction might take us into the curious inverse reciprocal relationship between conscious and unconscious processing as a function of threshold. We have suggested that this inverse reciprocal relationship can be understood as determining what is limited to conscious processing as contrasted with unconscious processing. From this standpoint the Snodgrass discovery of the ODT may open the door to investigations of the complex relationships between conscious and unconscious processing in normal and abnormal states.

Lastly, our findings may offer an opening for studying the neurophysiology of repression. The *ad hoc* results of the second study suggest that the repressive effect of the subliminal unconscious conflict primes is more closely associated with parietal alpha, while the alpha power effect of the supraliminal conscious symptom primes is more closely associated with frontal alpha. Also it seems that repression emerges as the outcome of complex interacting decisions and choices rather than as a punctiform cause acting at one particular time.

## CONCLUSION

We set out to seek evidence for a cause and effect relationship between unconscious conflict alpha power and conscious symptom experience. Our findings supported our hypothesis. Only when the unconscious conflict primes were subliminal did they have an inhibitory effect on the processing of conscious symptom targets, and this relationship was physiologically instantiated through inhibitory alpha power activity. The study also yielded unexpected findings concerning the effects of supraliminal conscious symptom primes. In both the initial and the new social phobic studies, the effects of conscious symptom primes and unconscious conflict primes appeared inversely related to each other. Specifically, in the new social phobic study, the unconscious conflict primes only produced inhibition when presented subliminally and only selectively for conscious symptom targets, while conscious symptom primes only produced inhibition when presented supraliminally, and did not discriminate between targets. We concluded that the supraliminal conscious symptom effects were due to conscious re-experiencing of the phobia with attendant efforts at conscious inhibition and avoidance, as occur in many cognitive phobia experiments. Only when subliminal unconscious conflict primes enter the picture is another level of meaning involved that engages repression. We can thus distinguish between conscious inhibition and unconscious repression, only the latter involving unconscious conflict.

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study demonstrated a cause and effect relationship between unconscious conflict and conscious symptom experience. In a subsequent exchange of letters the senior author accepted Professor Grunbaum's position. It was this agreement that led to the new study reported in the paper. There have been many contributors to the research and its execution whom we wish to acknowledge: James Bond, Richard Hertel, John Hartman (clinical judges); James Abelson, Ariane Bazan (co-authors of 2010 phobia study); ML Brown, (biosignal analysts); Beverly Knickerbocker, Adrienne Young (administrative assistant) who smoothed the way through many roadblocks, Brian Silverstein (research assistant) for his able development of graphs and figures; An earlier version of this paper was presented at the *Conference on the Freudian Unconscious: Between Neuroscience and Psychoanalysis*, Lausanne Federal Polytechnical School, sponsored by the Agalma Foundation, Lausanne, Switzerland, on October 29, 2011.

## SUPPLEMENTARY MATERIAL

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# Addiction and will

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A hypothesis about the neurobiological bases of drive, drive reduction and will in addictive illness is presented. Drive reduction seems to require both SEEKING and gratification. Will is the everyday term for our experience of drives functioning within us. Addictive drugs take over the will by altering neurotransmission in the SEEKING system. As a result of this biological change, psychological defenses are arrayed that allow partial gratification and reduce anxiety about the consequences of drug use. Repeated partial gratification of the addictive drive creates a cathexis to the drug and the drug seller. It also keeps the addicted person in a permanent state of SEEKING. The cathexis to the drug and drug seller creates a difficult situation for psychoanalytic therapists. The actively addicted patient will have one set of feelings for the analyst, and a split off set of feelings for the drug dealer. Addictive neuroses, which feature a split transference, are contrasted with Freud's concept of transference and narcissistic neuroses. For treatment of an actively addicted patient, the treater must negotiate the split transference. By analyzing the denial system the relationship with the drug dealer ends and the hostility involved in addictive behavior enters the transference where it can be interpreted. Selling drugs that take over the will is a lucrative enterprise. The addictive drug industry, about the size of the oil and gas industry worldwide, produces many patients in need of treatment. The marketers of addictive drugs understand the psychology of inducing initial ingestion of the drugs, and of managing their addicted populations. The neuropsychoanalytic understanding of addiction might be used to create more effective public health interventions to combat this morbid and mortal illness.

**Keywords: neuropsychoanalysis, SEEKING, drive, psychoanalysis, addiction, toxoplasmosis, cathexis, will**

## INTRODUCTION

*Toxoplasma gondii*, a single-celled protozoan parasite, manipulates the brain of the rat to shift their response to cat odor from defensive to sexual attraction (House et al., 2011). *Toxoplasma* in the environment gain entry into the rat by skin contact. They multiply in brain and muscle tissue. The immune response of the rat results in cyst formation.

The pathways for the defensive and reproductive pathways run in parallel from the olfactory bulb to the medial amygdala and hypothalamus in close anatomical proximity (House et al., 2011). *Toxoplasma* cysts elaborate tyrosine beta hydroxylase, the rate-limiting enzyme in the pathway from the tyrosine in food to dopamine. Prandovszky et al. (2011) found that infected brain cell cultures had a threefold increase in dopamine compared to uninfected cells. Alteration in brain dopamine results in a subtle shift in behavior. Rats infected with *T. gondii* shift their behavior from fearing/avoiding cats to approaching them as if they were desirable mates. The rats get eaten by the cats.

The organism makes its way into its preferred host, the cat, by taking over the brain of the rat (House et al., 2011). The rat behaves normally in all ways except that instead of avoiding cats, it seeks them out. This behavioral change is not for the survival of the rat, but for the survival of the *T. gondii* parasite.

The goal of this communication is to ask the question about whether a homologous process in the human has to do with the sale of addictive drugs. Like the process involving *T. gondii*, the mechanism would involve the dopaminergic system. The conclusion would be that, like the rat serving the *Toxoplasma* organism, the behavior of a human taking addictive drugs into their brain has to do with the benefit of the drug seller; even at the cost of the life of the addicted human.

There is almost no clinical material in this paper. Psychoanalytic and neuropsychoanalytic treatment of addiction has been extensively presented by the author in numerous clinical papers covering alcohol (Johnson, 1992, 1993, 2003a, 2011), marijuana (Jones et al., 2005), cocaine (Johnson, 2009a), heroin (Johnson, 1999, 2001, 2010), nicotine (Johnson, 2003a), and drug dreams (Johnson, 2001, 2003b, 2006, 2012) including papers describing whole psychoanalyses with 9-year follow ups after treatment for alcohol addiction (Johnson, 2011) and heroin addiction (Johnson, 2010). After 10 mostly clinical papers, this discussion focuses on the general implications of concepts derived from the confluence of neuroscience and clinical psychoanalytic work.

## DRIVE AND CATHEXIS: KEY CONCEPTS FOR ADDICTION NEUROPSYCHOANALYSIS

Drive and cathexis are concepts that originated during Freud's pre-psychoanalytic period of neuroscience research (Compton, 1983a). Since then, the field has struggled with the problem of how to combine clinical observational data with theoretical constructs that involve a completely unconscious aspect of motivation. Freud originally identified drive as the engine of relatedness, the primary conceptual device in psychoanalysis for explaining mind, body, and environment relationships (Compton, 1983b). For some

psychoanalysts, the concept of drive has taken on the extreme opposite quality. For example, Aron (1999, p. 259) stated, ". . .The classical drive/structure metapsychology . . . narrows our view of people, deprives them of subjectivity, and reduces them to objects. This limitation is true of any asocial, 'one-person' psychology."

On the other hand, drive or motivation has become a focus of the neuroscience approaches to addiction. For example, Kalivas and Volkow (2005, p. 1403) stated, "As the pursuit for the neural basis of addiction advances, it is clear that the search intimately involves understanding the neurobiological basis of motivation and choice for biological reward, such as food and sex, as well as more cognitively and experientially based reward, such as friendship, family and social status." Neuroscientists working in the field of motivation and volition have varying opinions as to the origin of motivation. Some reviews (Zhu, 2003; Haggard, 2008) look to cortical pathways as the initiators of actions. Others (Berridge, 2004; Kalivas and Volkow, 2005) focus on the dopaminergic pathway that leads from the ventral tegmental area (VTA) of the midbrain through the lateral hypothalamus to the nucleus accumbens as the central structural pathway involved in motivation. This is the SEEKING system (Panksepp, 1998).

In neuropsychoanalyst Jaak Panksepp's model, derived from his extensive experimentation with animals, the SEEKING system has the capacity to shift activity from one to another motivational system, depending on internal and environmental inputs. This supraordinate flexibility is exactly what Berridge (2004, p.201) cited against the drive model. "The most dramatic evidence against dedicated drive neurons came from studies of motivation by electrical brain stimulation. . . For example, if one stimulated the lateral hypothalamus of different rats, many rats might show eating behavior. But a few rats might show drinking behavior, a few show sexual behavior, or others show predatory aggressive behavior, depending on the availability of stimuli and on the disposition of the individual rat being stimulated." This phenomenon, that various motivated behaviors are prompted by one system, is exactly the concept of drive; a constant pressure from inside the organism to do work (Freud, 1915; Shevrin, 1997; 2003).

In an earlier contribution (Johnson, 2008) I considered addiction researchers Robinson and Berridge (1993), Berridge and Robinson (2003) distinction between "wanting" and "liking." In that paper I posited that Panksepp's SEEKING system is the same system that Freud (1915) hypothesized to exist deep in the brain, libidinal drive. My assumption was not based on a historical study. I was and am using Freud's thinking only because, in many cases, it is still the most perspicacious description integrating nomothetic neuroscience with ideographic psychoanalytic observation. I suggested that Freud's concept of the pleasure principle was connected to Panksepp's many observations of endorphin/opioid function in the brain (Panksepp, 1981, 1990, 1998, 1999; Panksepp and Watt, 2011, etc.). Importantly, the pleasure system is tied to the drive system via opioid receptors in the VTA and nucleus accumbens shell (NAS), where they potentiate glutamatergic and dopaminergic processes that intensify drive.

Using the SEEKING system to stand in for Freud's drive system obviates the objection that it excludes a focus on relatedness, since SEEKING and other instinctual systems, CARE, PLAY, LUST, and PANIC (Panksepp, 1998), offer a biologically based and much more articulated set of instinctual drivers toward forming relationships. It gives us a model for clinical work that preserves Freud's concept of libidinal drive while responding to Aron's concern that drive produces an "asocial, one person psychology." We SEEK relationships. Panksepp's neuropsychoanalytic formulation of instinct, which is based in animal research, solves problems which could not be understood by an approach that is purely based on clinical experiences with patients.

Freud described "cathexis" as an initially mobile instinctual energy that could be bound to persons, body parts, ideas, or dream elements (Freud, 1920, p.34). In the 21st century we have information that allows us to describe the neuroscience of libidinal investment (Johnson, 2008). Dopamine is released in the nucleus accumbens of mother rats following pup exposure. VTA or nucleus accumbens (drive/SEEKING system) lesions disrupt maternal behavior (Insel, 2003). Dopamine (D1) receptors are necessary for rats to develop place conditioning for opioids. Opioid receptor antagonists block the development of partner preference in rats after mating. Both drive and pleasure need to be functioning to produce attachment. Without the drive of the dopaminergic system, there can be no libidinal investment. In order to form a sexual bond, rats have to remember that mating was a pleasant, not just a driven, experience.

Other neural systems are involved when animals come to prefer specific mates. Medial orbital frontal, amygdalar, and hippocampal memory inputs are involved. Hormonal systems interact with drive and pleasure systems. Oxytocin potentiates endorphin release during mating. Oxytocin is essential for partner preference, as has been demonstrated repeatedly in experiments comparing the prairie vole, which has an oxytocin system, with the montane vole, which does not (Insel, 2003; Johnson, 2008). Prairie voles form sexual partnerships, montane voles do not. In summary, cathexis has to do with an ensemble of drive, pleasure, memory, hormones – but there is no cathexis without drive.

One conclusion of the 2008 paper was that versions of the 1993 Robinson and Berridge distinction between wanting and liking had already been discovered by previous investigators. Freud had described it in 1920 in his essay, "Beyond the Pleasure Principle." Panksepp had shown the distinction between wanting and liking in his papers on the SEEKING and endorphin systems (Panksepp, 1981, 1990, 1998; Panksepp and Watt, 2011, etc.). But the main conclusion of the paper was that in biological or "physical" (Johnson, 1999, 2003b) addiction, addictive drugs had changed the drive system so that they were urgently wanted; whether intoxication was pleasant or not. This conclusion is an elaboration of the concept that is generally accepted in the neuroscience community that addiction begins with an alteration in the mesolimbic dopamine system (Hyman et al., 2006; Koob and Volkow, 2010). Addiction represents the usurpation of neural processes that underlie pursuit of food, water, sex, and relationships. Implicit was an idea about cathexis that will be developed below; cathexis for drugs or drug sellers can complete with cathexis for people who are loved.

## DRIVE REDUCTION AND DRIVE

Why is the concept of drive reduction dead? I believe it is because Freud's thinking about this topic has been ignored by current neuroscientists. For example, when Berridge (2004) discussed why

drive reduction had been disproved by animal experiments, he explained that animals who only SEEK will do it forever, and animals who are only gratified, for example by having caloric requirements satisfied by gastric feeding, were still motivated to pursue food. An important source of his confusion is the behaviorist term "reward," which conflates the concepts of SEEKING/drive and gratification. It is only by separating these two components of drive reduction that we can understand how they operate.

Freud gave the fullest description of drive reduction in his 1923 paper, "The Ego and the Id" (Freud, 1923, pp. 21–23).

"Internal perceptions yield sensations of processes arising in the most diverse and certainly also the deepest strata of the mental apparatus. . .they are more primordial, more elementary than sensations arising externally. . .

Sensations of a pleasurable nature do not have anything inherently impelling about them, whereas unpleasurable ones have it in the highest degree. The latter impel toward change, toward discharge, and that is why we interpret unpleasure as implying a heightening and pleasure a lowering of energetic cathexis. . .

This something behaves like a repressed impulse. It can exert driving force without the ego noticing the compulsion. . . Not until there is a resistance to the compulsion, a hold-up in the discharge reaction, does the 'something' at once become conscious as unpleasure. . .

The part played by word-presentations now becomes perfectly clear. By their interposition internal thought-processes are made into perceptions. . . We are all 'lived' by unknown and uncontrollable forces."

The ego's relationship with the id, "Is like a man on horseback, who has to hold in check the superior strength of the horse. . . Often a rider, if he is not to be parted from the horse, is obliged to guide it where it wants to go."

Drive reduction involves a combination of the rapacious, insistent drive building to a state where it demands satisfaction, and the pleasure of complete gratification. Both must operate sequentially for the drive to be reduced. Drive alone, in the case of addiction the constant drive for addictive drugs, is only increased by exposure to drugs. Once addicted, exposure to alcohol, cocaine, nicotine, or opioids causes a brief diminution of desire, followed by an increase of the urgent wish for the drug.

In the case of self-stimulation of the drive center (lateral hypothalamus), animals wired to be able to activate this area will push the "on" button constantly until they die. The unpleasure of briefly relieved drive apparently causes endless fruitless attempts to achieve drive reduction. In contrast, pure gratification without activation of SEEKING is in the end unsatisfying. Pornography addiction may be an example of gratification that is endlessly unsatisfying. Masturbation may be unsatisfying because it gratifies sexually without engaging the SEEKING system. Apparently, animals or humans who can't reduce drive by combining SEEKING and satisfaction sometimes endlessly engage in activities that activate only one or the other half of drive reduction.

We have taken as a hypothesis that drive involves activation of the ventral tegmental dopaminergic SEEKING system running from the midbrain through the lateral hypothalamus to the nucleus accumbens. A second hypothesis is that drive reduction requires both activation of the SEEKING system and gratification; food, sex, a relationship, something that requires work (Freud, 1915; Shevrin, 1997), and involves the complete relaxation of gratification. Addictive behaviors cause a brief and incomplete reduction of drive that result in endless drug seeking. The Freudian concept of will is necessary to understand how drive and drive reduction operate in the individual to change behavior.

## THE CONCEPT OF WILL

In the Project for a Scientific Psychology (aka "Psychology for Neurologists") Freud explained, ". . .in the interior. . .there arises the impulsion which sustains all psychical activity. We know this power as the *will* – the derivative of the drives" (quoted/translated by Schmidt-Hellerau, 2001, p. 61). The experience of drives operating inside us can impel us to do things that we do not consciously "want" to do. This often leads to an interpretation by the analyst that certain behaviors are, "intentional but not conscious." The reasons that we do things are often not apparent to us.

In fact, the lay term "will power" sometimes seems to exist as a denial of true intention. People will say things like, "I wanted to eat the whole pint of ice cream, but I exercised will power and only had half." Or even less consciously, "I really wanted to stay on my diet and I struggled not to eat all that ice cream, but I did it anyway; I ate that ice cream against my will." Much of the work of psychoanalysis has to do with patients becoming conscious of their real motives, what the true goals of their will is (Wheelis, 1956; The philosophical and psychoanalytic intersection of will and drive was reviewed in Young and Brook, 1994).

As Freud said so presciently, it is the repeated stimulation of neuronal pathways that leads to cathexis (Schmidt-Hellerau, 2001, pp. 54–58). The process of facilitation of neuronal pathways, leading to structural changes in the brain, would nowadays be referred to as long-term potentiation (Kandel, 2006). The combination of experience and brain changes under the influence of neurotransmitters, neuropeptides, and hormones leads to the development of interests that are different for every person (Johnson, 2008). In other words, inborn givens take shape and definition through the interaction with the social environment and establish patterns of maintaining contact and relatedness with others. This phenomenon of modulation of cathexis by a combination of innate biology, development, and experience means that every person is a little different in their tastes. The urgent needs generated by the drive system, once specific tastes in object and patterns of relatedness become fixed, are matched up against external reality. The degree of pleasure and fulfillment resulting from actualization of one's drives and cathexes lead to either gratification or neurotic frustration (Johnson, 2008). In the case where expression of will leads to frustration, individuals feel that their life is not going well and yet are often not be able to articulate where the problem lies.

Interpretation of conflicts between conscious and unconscious goals, often described as "neurotic conflict," is the constant occupation of any psychoanalyst. Meissner (2005, p. 28) discussed "intrasystemic id conflicts" involving motivational systems. One might love one's mother consciously, and yet also wish to destroy her unconsciously. Both urges could be described as id-driven. This conflict generates anxiety – a signal that there is trouble in a relationship (Freud, 1926; Watt and Panksepp, 2009). There is

a conflict between the wish for additive drugs and the wish for relationships. Both could be characterized as id-driven.

In a typically parallel neuropsychoanalytic way, the intrasystemic id conflict of addiction can be seen psychologically and also neurobiologically. Psychologically, one might love one's mother consciously, and also unconsciously want to destroy her by destroying oneself with heroin. The use of addictive drugs can be understood as an unconscious expression of rage (Dodes, 1990). Neurobiologically, the conflict has to do with a conflict between urgently wanting a drug, and still wanting other goals of the drive system including a relationship with one's mother. The experience that the mothers of heroin users are wildly upset while the heroin user sees themselves is single-mindedly pursuing drug use, is an everyday experience on an addiction treatment service.

## HOW THE WILL IS TAKEN OVER BY ADDICTIVE CHEMICALS

There are only about 20 chemicals known to humans that alter the drive system so as to create a new drive (Johnson, 2008). These substances: alcohol, nicotine, benzodiazepines, opioids, stimulants, marijuana, phencyclidine, etc., all work by diverse mechanisms (Nestler, 2005), but with the same uniform end result. They cause sensitization of the ventral tegmental dopaminergic SEEKING system to the chemical (Robinson and Berridge, 1993). After sufficient exposure to the chemical, the person begins to want the drug; irrationally and insistently.

There is a triangle on the lower right half of **Figure 1** which shows the hypothesized mechanism of physical addiction for stimulant drugs. The corners of the triangle are the VTA, the NAS, and the prefrontal cortex. Cocaine and methamphetamine increase

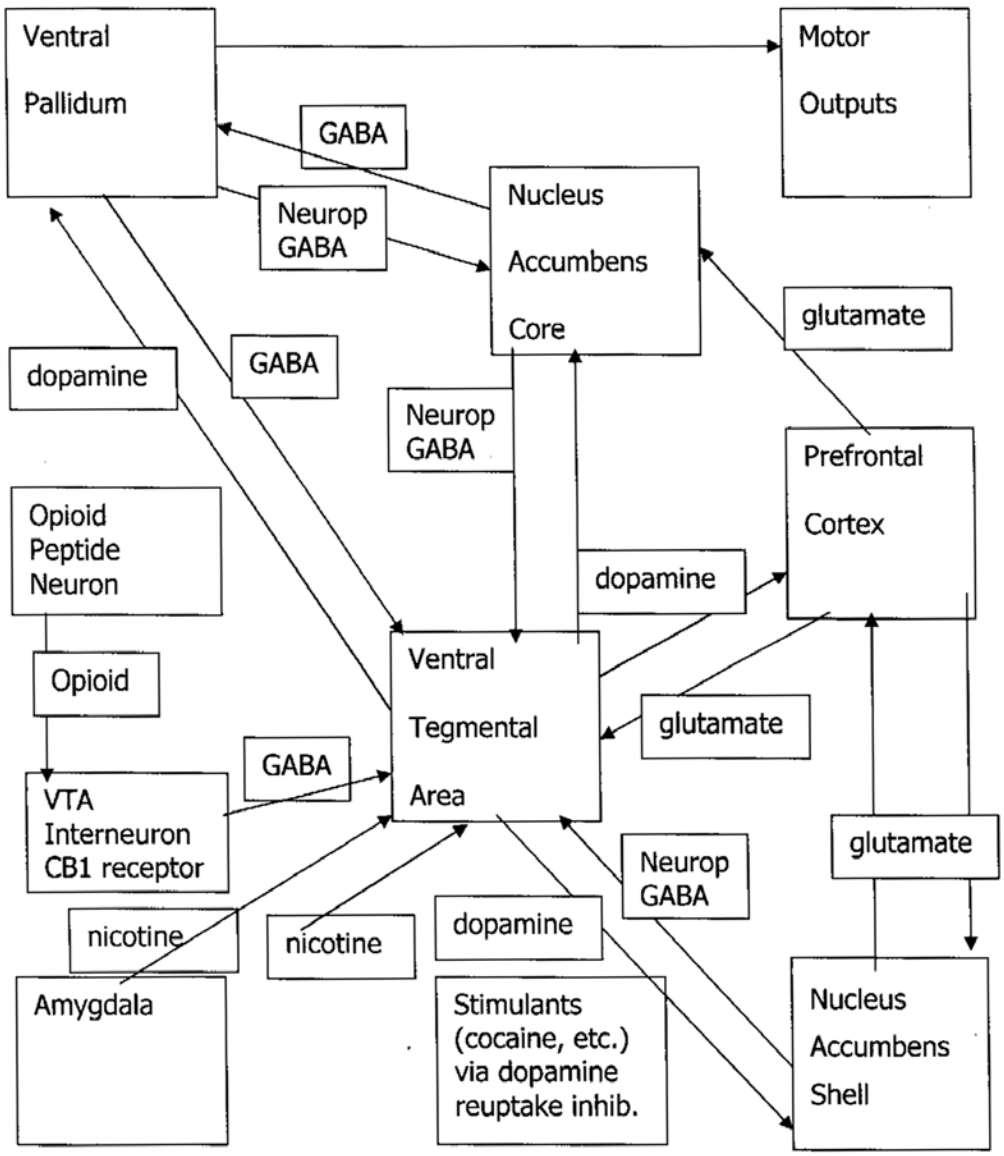


**FIGURE 1 | Craving/dreaming pathways: Neurop, neuropeptides; GABA, gamma amino butyric acid, CB, cannabinoid.**

dopaminergic neural activation from the VTA directly to the NAS (Niehaus et al., 2009) by blocking the dopamine reuptake transporter protein. Nicotine has receptors on the VTA, and stimulates activating signaling from the amygdala (Nestler, 2005).

There is a tonic brake on the VTA created by GABAergic inhibition by a set of interneurons. This set of interneurons is represented by a box directly to the left of the VTA box that occupies the center of **Figure 1**. Opioids act as a brake on an inhibitory system involving GABAergic interneurons that slow dopamine neurotransmission from the VTA to the NAS (Nestler, 2005). Removing this inhibition from the VTA results in increased dopamine activation of the NAS. Marijuana's tetrahydrocannabinol lodges in endocannabinoid receptors in inhibitory GABAergic VTA interneurons, inhibiting this brake so that there is increased dopaminergic stimulation of the NAS (Fattore et al., 2008). The mechanism for alcohol and benzodiazepines may be that in withdrawal from these GABAergic drugs, there is a lessening of GABAergic inhibition of the VTA, and dopamine neurotransmission is increased (Enoch, 2008).

The mechanism of physical addiction for every addictive drug is that dopamine neurotransmission from the VTA to the NAS is altered. Craving, the psychological manifestation of dopaminergic drive activity in this pathway (Shevrin, 1997), is induced by drug exposure. After repeated exposure to the addictive chemicals that produce dopaminergic activation of the SEEKING system, the chemicals become wanted, desired, craved; just like so called, "natural reinforcers," food, water, sex, and relationships.

The pathway does not end with the NAS. As seen in **Figure 1**, there are limbic and frontal centers connected with this subcortical pathway. As the effects of stimulation in the subcortical pathway cause long-term potentiation of higher centers, and drugs are wanted, drug cues recognized at pathways involving amygdalar, hippocampal, and frontal activation provoke neural firing, and downgoing glutamatergic pathways increase craving by stimulating more dopamine release. The higher centers notice possible availability of drugs, and turn up craving.

The pathways in **Figure 1** allow for the concept that there are two mechanisms of induction of craving; the "upper" and the "downer" pathways. The terms "upper" and "downer" are street language for whether the user experiences a drug as activating or relaxing. These terms may also reflect a difference in neurobiological action. The upper pathway, activated by cocaine, methamphetamine, and nicotine, directly increases firing from the VTA to the NA. The downer pathway is less direct. The interneuron braking system is deactivated, leading to increased activation of VTA to NAS dopamine. This would account for the fact that the upper drugs cause drug craving so commonly and are harder to become abstinent from, while downer drugs such as marijuana, alcohol, opioids, or benzodiazepines provoke addiction with lower frequency. When drugs in the downer group are used for recreational or medical reasons, most users do not become addicted.

Persons whose brains have been changed by addictive drugs must obtain the chemical or they are punished by ferocious unpleasure if there is, "A resistance to the compulsion, a holdup in the discharge reaction." These chemicals are used to take over the will of the victim. For example, one might say that the person who is smoking a cigarette while having fantasies of dying of cancer, heart disease, or emphysema is not following their own will, but actually enacting the desire of the cigarette manufacturer, who is selling the cigarettes.

We might say that human children, who begin using nicotine on average in the United States at age 13, are controlled by a process homologous to rats infected by toxoplasmosis. Their behavior has been subtly altered by a change in dopamine/SEEKING. They behave in almost every way as if they are themselves. But inhaling nicotine, along with particles that can produce cancer or ruin the lung's ability to obtain oxygen, is in the service of the cigarette sellers.

## DRUG-INDUCED RELATIONSHIPS

By using these drugs, individuals begin to "want" them for no reason other than brain changes. By associative learning, the purveyors of the drugs are also wanted. The state of drug craving is intensely emotional, urgent, energetic, searching for a means of gratification. By providing the drug, the seller becomes wanted, cathected.

Relationships with drug providers can have a yearning, romantic cast. As one patient told me, despite being in treatment for addiction, and sober, "I love my dealer!" A patient with attention deficit hyperactivity disorder (ADHD), cocaine and nicotine addiction suspected I would profit from having him buy a prescription for the antidepressant bupropion, used to treat ADHD and nicotine dependence. This suggests a transference from his drug sellers to me, with their/my drug as the intermediary causing a cathexis. A third patient, early in his treatment for opioid addiction, called the drug dealer to whom he had paid $200,000, his "best friend." When in emotional distress, my patient refused to call my cell phone, but rather, kept relapsing because he would call his drug dealer's cell phone.

There are secondary changes in the brain as addiction progresses. Later brain changes involve routinization of drug SEEKING by reorganization of pathways (Koob and Volkow, 2010) involving the nucleus accumbens core (Everitt and Robbins, 2005; Kalivas and Volkow, 2005) and diminished prefrontal inhibition (Bechara, 2005), especially if there are losses of brain tissue due to the various degrading effects of these drugs (reviewed in Johnson, 2009b). The longer addiction goes on, the harder it is to recover. Initiating brain changes with one drug results in faster adaptation with craving for a second addictive drug (Robinson and Berridge, 2000). For example, individuals who start smoking cigarettes before the age of 15 are 80 times more likely to use illicit drugs (Lai et al., 2000).

Exposure to addictive drugs can cause brain changes that result in permanent craving. This makes perfect sense if you think of the reason that drives are built into animals. We need to have a steady pressure to obtain items in the environment that are related to survival. If we learn where these items are, or how to recognize their possible availability, we need to have our craving turned on at that moment when we recognize availability cues so that we intensify our search for the proximal, life-supporting item, no matter how long ago we learned about the linkage between cue and drive goal. After learning about the constant availability of reward in the environment, SEEKING them can become a more automatic,

unconscious behavior – modulated in the nucleus accumbens core.

However, this survival mechanism has its drawbacks. One Freudian discovery was that this constant pressure to act can come into conflict with other considerations that have to do with living in a social environment. The original paradigm of the Oedipus Complex was the conflict between the sexual drive and the presence of a larger, older, same-gender parent who was in the way of the child's closeness with the parent of the opposite gender (Freud, 1909).

Conflict is also generated regarding drug-seeking. Once addictive drugs get entrained into the drive pathway, there is a constant pressure to act to procure the drug experience again, no matter how unpleasant and dysfunctional the consequences. This is no different conceptually than yearning for a parent of the opposite gender when one is too young to effectively or safely compete. Lust can be dangerous; whether for love or drugs. Life provokes internal conflict.

Drives are so deeply unconscious that it is hard to experience them directly. Describing "craving" is a difficult task (reviewed in Johnson, 2012). Craving seems absent 1 min, overwhelming the next. An unconscious basal state may be altered by the provocation of dopamine neurotransmission in the VTA/nucleus accumbens pathway when drug cues activate frontal or limbic centers. With a drug cue or intense emotion, the previously unconscious drive enters awareness.

Finally, just as food, water, sex, and relational needs provoke dreams, so does the hunger for drugs (Johnson, 2001). Drug dreams are a unique aspect of physical addiction (Johnson, 2003b). Craving for drugs that is not conscious can be made conscious by the interpretation of dreams (Johnson, 2001).

## PSYCHOLOGICAL SEQUELAE OF PHYSICAL ADDICTION

As soon as the drug has had sufficient impact on the neural pathways shown in **Figure 1**, there is a reorganization of thinking. We are in a position to actually see the impact of physical factors in the brain on psychology by talking to persons who have undergone this change. The victim of this process begins to have the experience described above that they become uncomfortable as the drug washes out of their brain. The addicted person has that inner sensation that they absolutely must have more of the drug to ward off the unpleasure of craving. They suffer from endless drug SEEKING. Persons with alcohol dependence show up at the bar at 8 am. Persons with heroin dependence knock on their dealer's door early in the morning. Cigarette smokers get off planes and have a cigarette before they do anything else. The unpleasure of craving is so intense that addicted individuals do everything they can to get rid of it. But it always comes right back.

Defenses are arrayed by the ego to modulate the new drive state. Consistent with Freud's metaphor of horse and rider (quoted in the drive reduction and drive section), the newly addicted person urgently wants to procure and use their drug. Their ego is aware of the potential liabilities in using it again. The ego deploys a series of explanations about why using the drug again is, "OK."

Psychological defenses reduce anxiety at the expense of obscuring reality. It is customary in the field of addiction to talk about "denial." However, there is no reason that a single defense, denial, would be arrayed against a drive. There are as many defenses arrayed against the drive for addictive chemicals as there are against any other drive. For example, an addicted person might use projection of responsibility, "I'm using because she/he treated me badly." The defense could be minimization, "Going to work late because I was hung over from drinking isn't such a big deal."

Each person's denial system is their own unique set of explanations about why they should keep using their addictive drug(s). To the outside observer, their denial system, the particular set of psychological defenses set up to protect continued dangerous drug use, makes no sense. This is because the defenses are arrayed against internal stimuli. The observer cannot feel the drive to use the drug. In fact, one of the problems of identifying with addicted individuals is that the observer or psychoanalyst usually has not had the patient's experience of pursuing drugs. The best way to make an empathic identification is to imagine one of the basic drive goals, such as food. One can think about how hard it is to lose weight by tolerating the urge to eat things that are off the weight-loss diet. One will notice that defenses are arrayed to protect eating foods that are not consistent with the diet, just as addicted persons have defenses about using when they also wish to be abstinent.

The denial system of the physically addicted person is based on their craving for the drug, and on their allegiance to the seller of their drug. This may sound like an odd claim; isn't the drug the object? The answer to this question puts us back where Freud started. Human relationships are grounded in the gratification of drives. In adult sexual relationships, attraction leads to increasing involvement, sexual gratification, cathexis, and loyalty.

We can understand how drive precedes cathexis in relationships if we observe the SEEKING system functioning with the drive for addictive drugs. Persons who become addicted develop an allegiance to the seller of the drug. Cigarette manufacturers are keenly aware of cathexis. Their goal is to make the user of cigarettes fall in love with the brand that contains their nicotine.

In the United States, about 20 million persons buy illegal drugs, and it is almost unheard of for an addicted person to turn in their drug dealer. In part this is because the drug users fear that they will be killed if they alert police that their dealer is selling drugs. But mostly it comes from cathexis. Addicted persons have warm feelings toward their dealers; even as they may also fear being killed by them. Warm feelings that cover a fear of being killed is the defense, "idealization."

Craving provokes idealization. Idealization of the drug is a constant and indispensable part of denial. This defense, as described by Klein (1957), involves fear of the object (drug/drug seller). Addicted people are terrified by their behaviors. Yet this information is unavailable to them consciously. Their conscious experience is that, whatever the drug, its use is wonderful. People who smoke cigarettes are staying slim, being free to defy authority, expressing their emotions, and their sexuality – just like cigarette smoking actors do in the movies. Some persons addicted to alcohol pride themselves on how much they can drink. Some users of heroin feel that it is a cooler drug than any other. For addictive drugs that are legal, advertising has the theme of ideal behavior; that the drug or alcohol is connected with social dominance or pleasure in sports or relationships. I summarize various

aspects of this idealization in **Table 1** (explained at length in Johnson, 1993, 1998).

Idealization, like laughter, is catching. This may be an underlying dynamic of the social nature of the spread of cigarette smoking (Christakis and Fowler, 2008). When a 12-year-old child sees a 16-year-old child smoking a cigarette, the 16-year-old is using idealization internally to defend against their panic about seeing how out of control their behavior is and to defend against their perception of physical changes such as cough and shortness of breath. This idealization is represented to the 12-year-old interpersonally. The 16-year-old idealizes their ability to smoke a cigarette without having to cough when the irritating smoke enters their lungs, an aspect of tolerance. They communicate to the 12-year-old that smoking is appealing, "cool." As a result, the 12-year-old victim will tolerate the aversive aspects of smoking until tolerance, craving, and denial set in. This victim is then in a position to pass the addiction on to another young victim. Other drugs work by the same mechanism. It doesn't matter what the chemical is, the defense of idealization is uniform for addictive drugs.

## TREATMENT IMPLICATIONS OF THE NEUROPSYCHOANALYTIC CONCEPTS OF DRIVE, DRIVE REDUCTION, AND WILL

Freud had a set of conditions that he felt had to do with the distribution of libido by the ego. In the "transference neuroses" libido was available to be cathected to the analyst. This was ideal for psychoanalytic treatment. In the "narcissistic neuroses" (Freud, 1917, pp. 420–423) libido was withdrawn from objects, therefore from the analyst, and psychoanalytic treatment was impossible. As a hypothesis, we could add to this list "addictive neuroses." Some libido is cathected to the drug/drug seller, some to other people – including the analyst. There is a splitting of the transference, just as there is a splitting of the patient's experience (**Table 1**). What the analyst observes is that the patient has many ordinary dynamic interactions in the hour, but keeps the addictive urges outside the hour.

The patient does with the analyst (of course) what they do with all relationships. The patient very much wants to be engaged with the analyst, but has another cathexis for her/his libido that has nothing to do with the analyst. The patient's conscious experience is that behaviors having to do with obtaining and using drugs have little to do with other relationships. Their libidinal investment is dissociated into the part that cares deeply about the analyst and the part that cares deeply about obtaining and using drugs.

One result of this situation is the familiar complaint of some addicted individuals who claim that their psychoanalysis did nothing to change their addiction. This is because the patient felt that their addiction had nothing to do with their analyst (their true experience) and their analyst was not in a position to hear about the effects of the addictive drug. In these psychoanalyses, the patient and analyst worked on their relationship, while the relationship with the drug/drug dealer remained unexamined. The unintended result of this approach can be that the patient who has completed such a psychoanalysis is even more adept at having relationships with people while using their drug addictively. Lying midway between the transference neuroses and the narcissistic neuroses, the addictive neuroses require some alterations of technique in order for the patient to benefit from treatment.

What can an analyst do when faced with an addictive neurosis that has a split cathexis/transference? The answer has something to do with developing conscious conflict about drug use within the relationship with the analyst. The patient knows that they are in trouble because of their relationship with the drug and with the drug dealer, but not consciously. The patient knows that they cannot both fully engage in the relationship with the analyst, and stay involved with the drug/drug dealer, but not consciously. The relationship with the drug/drug dealer is based on a system of beliefs which make perfect sense to the patient because they exist to diminish the anxiety about using a drug that is creating damage and may result in death. For example, many persons who are addicted to nicotine will say things like, "Sure cigarettes may kill me. We all have to die some time!"

Therefore, in many cases the analyst will have to divide the treatment into two phases. In the first, the transference is not explored because it is split. The analyst appreciates that attacking the relationship with the drug/drug dealer is not going to work. A strong cathexis has been established after many experiences of great unpleasure relieved by drugs and/or alcohol. The analyst limits their interventions to clarifications and confrontations that intensify conscious conflict between the wish to use and the symptoms of addiction that ensue from use. By using these non-transference interpretations, the analyst works on the denial system. It is only after the patient has moved through the "stages of change" by virtue of increasing dismay about the consequences of drug and/or alcohol use, and stopped using, that the treatment enters the second phase.

Addicted persons are like children in a divorce who don't want to tell one parent what is going on with the other. They feel an alliance with both, but understand that the allegiance to one is

**Table 1 | Addictive idealization/splitting.**

| The addiction | |
|---|---|
| **Experiencing ego/psychic reality** | **Observing ego/external reality** |
| Facilitates relationships | Makes close relationships difficult (wards off fear of control/merger) |
| Creates pleasure | Creates pain |
| Gives a sense of omnipotence | Makes one impaired |
| Is a rebellion that creates a feeling of separateness | Is a compliance with the attacking introject that undercuts the use of aggression needed to be separate |

essentially disloyal to the other. Just as one divorced parent often does not hear what the child is doing with the other, the analyst often does not hear what is going on with the drug dealer. Not being open and honest is the result. This formulation allows the treating clinician to shift from, "My patient lied to me," to, "I encountered a split transference." The first reaction might produce anger, the second interest, and a feeling of a technical challenge.

For any psychotherapy treatment, a key ingredient of healing has to do with the therapeutic alliance (Nissen-Lie et al., 2010). If addiction therapists use non-specific or intuitive interventions that are warmly related, outcomes might be the same despite different theoretical orientations. Therapists who intuit the underlying neuropsychodynamics more accurately might have better outcomes, but be unable to explain why. For the therapist who was able to explain what they were doing with neuroscience and metapsychology, there might be better outcomes – but this hypothesis has not been empirically tested.

An innovative psychoanalytic treatment of alcohol use disorders in borderline personality disorder, Dynamic Deconstructive Psychotherapy, subjects showed a significant decrease in heavy drinking accompanied by complete cessation of other drug use. In contrast, subjects in optimal community care received more treatment but showed increased drinking and increased drug use over the 30 month post-treatment follow up study (Gregory et al., 2010). This kind of naturalistic comparison of outcomes for patients who are initially randomized into neuropsychoanalytic or conventional treatment groups would be a way to empirically test the concepts described here.

Talking with patients during active addiction, one becomes aware that use is procedural, automatic, unconsidered. The technique of the first phase of neuropsychoanalytic treatment of addiction is to sharpen the conscious conflict between the drive derivative that is in evidence during use, but not conscious, and the ego's alarm at the reality of the consequences. Caring is communicated. Denial is undercut. We must remember the earlier quote from Freud regarding the function of word-representation as the mechanism by which internal unconscious thought processes are made into perceptions. In order for the addicted person to continue to be actively addicted, they can't think about what they are doing. Talking about one's urge to use drugs and alcohol takes place within a relationship. As Freud said about word presentation, "It is like the theorem that all knowledge has its origin in external perception.... A hypercathexis of the process of thinking takes place, thoughts are *actually* perceived – as if they came from without – and are consequently held to be true" (Freud, 1923, p. 23). Talking about craving and addictive behaviors changes them from precontemplative unformulated experience to more conscious problems that require work in psychotherapy.

If the goal of the ego is to serve the id, like the rider guiding the horse where it wants to go, then the patient will resist talking about their addiction because it disrupts the ability to go get drugs. In this way, the powerful urges created by exposure to addictive chemicals debilitate ego functioning. This impairment is often experienced by the analyst as having a patient who says, "Nothing comes to mind," or who does not arrive for treatment. Recognition of this injury to ego functioning by an altered drive state can be ameliorated by interpreting the lack of association or the missing of appointments as manifestations of craving. For example, the analyst may respond to a patient who says, "Nothing comes to mind," with, "Perhaps you are thinking about using drugs, and you are trying NOT to talk to me about that."

The psychoanalyst should not take idealization at face value. A patient who romances their addictive behavior can be listened to until the negative/frightened side of the thinking emerges. The alternative to addictive idealization is conscious ambivalence.

What happens when the denial system is interpreted sufficiently so that the patient stops using? My observation is that the split transference collapses, and the issues that had been diverted into addictive drug use enter the transference. I reported, "The psychoanalysis of a man with active alcoholism," where the end of alcoholic drinking during days per week psychoanalysis resulted in intense hostility entering the transference (Johnson, 1992). In the second phase of treatment, aggressive derivatives (Dodes, 1990) that had been expressed through the use of alcohol entered the transference relationship, where they were explored and ameliorated (Johnson, 1992). For some patients, when addictive behavior stops, the analyst has to be prepared for a siege of hostility that had never been in evidence during the first phase of treatment. The addictive behaviors had expressed the hostility and displaced it away from the transference.

I reported the 4 days per week psychoanalysis of a man with heroin addiction where cessation of heroin use resulted in an intense anaclitic depression entering the transference (Johnson, 2010). The patient went from a cool, unrelated person to an intensely needy and frightened person. The amelioration of the anaclitic depression within the transference resulted in a 9-year absence of addictive symptoms at the time of the report.

## PUBLIC HEALTH APPLICATIONS OF THE NEUROPSYCHOANLYTIC MODEL

Psychoanalysis has been since its early days a theory of culture as well as of the individual mind (Paul, 2011). The discussion so far has described an illness that is based in a brain system that is deeply unconscious. Items that impinge on the drive pathway are "needed." Addictive drugs are a commodity. The property of these drugs, that they take over the will by creating dysphoria/craving/unpleasure during abstinence, means that addicted persons will do just about anything to obtain their drug.

How widespread is addiction, and how much money is involved in addiction? Let's think about the number of brains involved. 26% (World Health Organization [WHO], 2010) of the world's population of almost seven billion smokes cigarettes. This amounts to about 600 billion cigarettes/year sold (World Health Organization [WHO], 2008). 13% of the world's population drinks at least 40 g of alcohol (three drinks) per day (World Health Organization [WHO], 2010). There are nearly two billion people using nicotine and one billion people drinking substantial amounts of alcohol.

The amount of money involved in selling legal drugs seems not to be carefully tracked worldwide. We know facts such as Philip Morris International was the 14th most profitable company in

the United States in 2008, making $6.89 billion in profits (CNN-Money.com 2010). The United Nations Office on Drugs and Crime (United Nations Development Programme, 1999; Reuter et al., 2009, p. 3) estimates that the illicit drug industry accounts for 8% of world trade, about the same size as the oil and gas industry or world tourism. Drugs that impinge on the SEEKING system have many customers.

How lethal and morbid are drugs and alcohol? Worldwide tobacco accounts for 9% of all deaths, 18% in high income (>$10,000 US) countries (World Health Organization [WHO], 2010). Alcohol causes 4% of deaths worldwide, 2% in high income countries (World Health Organization [WHO], 2010). Alcohol is the #3 leading global risk for burden of disease behind starvation and unsafe sex, and tobacco is #5 (World Health Organization [WHO], 2010). Cigarettes kill about half of the persons who use them (World Health Organization [WHO], 2008), which adds up to 443,000/year in the United States (Centers for Disease Control [CDC], 2009) and about four million/year in the world (World Health Organization [WHO], 2008).

How would we account for this apparently "irrational" economic activity? The SEEKING system of cigarette smokers has been captured by nicotine. If a seller can induce a potential victim to expose their brain to an addictive drug a few times, the alteration in the drive pathway will make the person want the addictive drug despite the danger. For this reason, purveyors of addictive drugs use a sophisticated psychological understanding of idealization and splitting to attract and manage their customers. For example, the nephew of Sigmund Freud, Edward Bernays, and one of the founders of American psychoanalysis, A. A. Brill, went to work for American tobacco companies in the 1920s to help with campaigns to attract new populations to the smoking of cigarettes (Brandt, 2007).

Many smokers say that they don't want to smoke, even though they show that they do want to smoke. Whose will are they following? The addicted person is following the will of the seller. While the smoker knows they cannot possibly benefit from their addictive behavior, the entire industry of production, marketing, and sales benefits enormously. This is true of any industry that produces a chemical that becomes urgently wanted by altering the drive pathway; whether a government deems that chemical legal or illegal.

We may be attracted to many people, but we make relationships based on cathexis. We fall in love with people who can meet our needs; conscious or otherwise. Love is irrational. The addictive drug industry is successful by capturing the will and the cathexis of its victims.

This information is of value in combating addiction. Public health initiatives informed by concepts such as the capture of will and cathexis, idealization of drug use, and the financial consequences of having a commodity with these properties, would lead to much different behavior by governments. For example, the addictive drug industry might be nationalized to divert money away from those who profit by deceptive advertising to teenagers, and to properly inform the public about how addictive drugs work in the brain to produce bizarre behaviors. It is more desirable from a harm reduction standpoint to have heroin sold in state stores by drug counselors than by gangs on the street with guns. It is more desirable from a harm reduction standpoint to have methamphetamine profits go to government revenues than drug cartels.

Finally, returning to the idea of the homology of the way that *T. gondii* controls the brain of the rat, and the way that protagonists of the addictive drug industry control the brain of the addicted customer, we notice that in both cases there are examples of random collateral damage. Toxoplasmosis is an important human disease, affecting about 1/3 humans in the world (House et al., 2011). There is no particular advantage for the *Toxoplasma* to inhabit the human brain since the organism dies there when the human dies.

There is speculation that the parasite expresses dopamine in the human brain, producing in some hosts schizophrenia or obsessive compulsive disorder (House et al., 2011). The dopamine blocker haloperidol moves the behavior of both humans and rats back toward normal. It completely abolishes the rat's interest in cats and restores their normal fear (Prandovszky et al., 2011).

It may be that while there are many individuals in the addictive drug industry who consciously manipulate the brains of their customers, there are other individuals such as physicians who are mystified by the way their attempts to help patients with pain or anxiety using medications in the opioid and benzodiazepine classes results in addictive behaviors. Patients who were initially grateful for the help of the physician later begin to manifest manipulative and hostile drug-seeking behaviors that cause consternation in the physician. It may be that without thinking about this process, physicians are seeding their patient population with medications that may become urgently wanted by some who undergo the brain change described here. This formulation about how drugs alter the will may facilitate more careful prescribing.

## SUMMARY

Combining developing concepts about the brain effects of addictive drugs with psychoanalytic observations, new hypotheses about the disease of addiction have been generated. Addictive drugs take over the will by transiently increasing dopamine firing in the SEEKING pathway. A new drive to obtain the drug results in the formation of a series of psychological defenses that both promote gratification and shield the person from the anxiety produced by addictive behaviors, the denial system. Idealization of the drug is a ubiquitous defense. Addicted persons cathect the seller of the drug as a result of repeated gratification of the drive. They fall in love with the drug and the seller/dealer.

The first task in treating actively addicted patients involves negotiating the split cathexis. The treater rides the line between ignoring the addiction, and directly opposing the cathexis with the drug/drug dealer. Clarification and confrontation are the two main types of interpretation that are used until alcohol or drug use ceases.

After cessation of use, the treater has to explore underlying hostile/aggressive urges and dependency needs that had been encapsulated by the addictive behavior. It is rare to see a purely physical addiction. In most cases, the very reason that the addiction was adopted has to do with an inability to use aggression effectively to negotiate relationships and inability to depend on people. Without a thorough exploration of these dynamics, the patient is prone to relapse to use of the addictive drug.

Selling addictive drugs is a huge industry in the world. Sellers use their understanding of the psychodynamics of addiction to capture brains. A public health approach can use the formulations above to help potential victims understand that the drugs work by taking over the will and causing warm feelings toward individuals who don't mind having their customers die.

The author has suggested a homology between the way the *T. gondii* parasite takes over the will of the rat, and the way addictive drugs take over the will of a person. In both instances "the will" involves dopaminergic function. One aspect of the behavior of the victim involves being willing to sacrifice their life to propitiate the welfare of the parasite or the welfare of the drug dealer.

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GENERAL COMMENTARY
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# EEG-Neurofeedback in psychodynamic treatment of substance dependence

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**A commentary on**

**EEG-neurofeedback and psychodynamic psychotherapy in a case of adolescent anhedonia with substance misuse: Mood/theta relations**
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The relationship between therapeutic techniques and psychoanalytic theory is complex and defies a direct translation from theory to practice. However, especially in recent years, there have been increased efforts to bolster psychodynamic research by drawing on neuroscientific findings. Proponents of this approach argue that the so-called "neuropsychoanalytic" models are only drawing upon Freud's own originally neurological framework- reflecting one of the central disciplinary origins of psychoanalysis (Kaplan-Solms and Solms, 2000). Indeed, Freud considered his psychologically based models a temporary structure which would later be reinforced once mechanistic neurological processes were identified which corresponded to the psychological processes he described. While not entering the specifics of this claim, it is reasonable to suggest that the brain-mind relationship has always been fundamental to psychoanalysis but this relationship has not been exploited within its clinical techniques.

One means of further exploring the real time relationship between psychodynamic clinical processes and their manifestation in neuroprocessing is the integration of neurofeedback into psychodynamic sessions. Practically speaking, both interventions could be integrated, or at least inform one another. How this could be done is yet to be established.

We would recommend that the interventions are done in parallel, for the neurofeedback protocols address cognitive dysfunction sensory-motor rhythm (SMR) and well-being (A/T) so that more is gained from the psychotherapy which is necessary from the outset to provide psychodynamic support. For logistical reasons all three were done in an afternoon in our study but with hindsight this proved too taxing and separate sessions for all three would be recommended. Neurofeedback (NF) can be characterized as a form of instrumental learning using feedback in real time from the brain's electrical activity. Participants learn to regulate their brain activity themselves through a process of repetition and reinforcement (Gruzelier, 2012). NF training has been shown to be an effective tool to aid in the treatment of a wide range of psychiatric disorders. For one example, a substantial body of research has been conducted over the past three decades by Peniston using a slow EEG-wave protocol for the treatment of addictive disorders (Peniston and Kulkovsky, 1999). This "Peniston-Protocol" became very popular and widely accepted as a research paradigm and has shown to be effective in a number of studies (Scott et al., 2005; Sokhadze et al., 2008). Substance use disorders result in specific alteration in brain activity that is detectable with the use of quantitative electroencephalography (EEG) methods (Peled, 2008). Psychodynamic psychotherapy aims to identify and modify these enduring patterns of thoughts, feelings, impulses, and defenses that, in turn, lead to maladaptive compromises, ineffective behavior, and conflicts in interpersonal relations (Shafranske, 2009). So the therapeutic question is in which way the altered brain activity can be normalized by either NF, psychodynamic therapy or the combination?

To further illustrate this we refer here to very limited data coming from a single case treatment of a student who, on a weekly basis throughout a university term, was given short-term psychodynamic psychotherapy and two EEG-neurofeedback protocols: SMR and alpha/theta (A/T) (Unterrainer et al., 2013). Substance misuse produces a diversity of EEG irregularities; there is no characteristic pattern. Accordingly neurofeedback therapy has focused on remedying the cognitive and affective deficits such as attention, impulsivity, anhedonia, etc. Our case study approach was informed by Scott et al. (2005) who preceded A/T training with the a course of SMR training (see Egner and Gruzelier, 2001) reporting a beneficial outcome from the combined neurofeedback protocols on impulsive errors and reaction-time variability in a sustained attention task, aside from a reduction in alienation, depression and defensiveness. Here we attempted to treat a long term drug misuse habit co-occurring with a depressive mood disorder (Lewis et al., 2008). In this single case psychodynamic psychotherapy

sessions were always applied right before the Neurofeedback training on the same day. As a result the patient's capacity for attention as evinced by application to course work in English literature, improved substantially, and there was a striking reduction in psychopathology. The improvement was much more rapid than we would have anticipated from either therapy alone. This tentative finding suggests a number of avenues for further exploration. For example, given the increased interest in the neurobiological foundations of psychoanalytic theory, EEG-neurofeedback could potentially also be used to understand therapeutic change processes (Linden, 2006). Exactly how that would be achieved, would require a repeating combined NF/ psychodynamic treatment approach in order to observe, how the NF learning outcome differs between positive and negative therapy outcomes. In order to confirm the interaction effect of these combined therapeutic interventions a randomized controlled trial would be necessary. Another recommendation would be to schedule the psychotherapy and neurofeedback sessions on separate days and also schedule the SMR and A/T protocols on different days. There are studies from other groups which have tried to combine neurofeedback and psychotherapy (Arns et al., 2009), however, to our knowledge this case is the first one, in which Neurofeedback was related to a strictly psychodynamic approach and certainly the first for drug misuse. Hopefully future studies will confirm our initial impression in order to further develop a NF informed model of psychodynamic psychotherapy, and to apply this beyond cases of substance misuse.

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# A clinical case study of a psychoanalytic psychotherapy monitored with functional neuroimaging

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This case study describes 1 year of the psychoanalytic psychotherapy using clinical data, a standardized instrument of the psychotherapeutic process (Psychotherapy process Q-Set, PQS), and functional neuroimaging (fMRI). A female dysthymic patient with narcissistic traits was assessed at monthly intervals (12 sessions). In the fMRI scans, which took place immediately after therapy hours, the patient looked at pictures of attachment-relevant scenes (from the Adult Attachment Projective Picture System, AAP) divided into two groups: those accompanied by a neutral description, and those accompanied by a description tailored to core conflicts of the patient as assessed in the AAP. Clinically, this patient presented defense mechanisms that influenced the relationship with the therapist and that was characterized by fluctuations of mood that lasted whole days, following a pattern that remained stable during the year of the study. The two modes of functioning associated with the mood shifts strongly affected the interaction with the therapist, whose quality varied accordingly ("easy" and "difficult" hours). The PQS analysis showed the association of "easy" hours with the topic of the involvement in significant relationships and of "difficult hours" with self-distancing, a defensive maneuver common in narcissistic personality structures. In the fMRI data, the modes of functioning visible in the therapy hours were significantly associated with modulation of the signal elicited by personalized attachment-related scenes in the posterior cingulate ($p = 0.017$ cluster-level, whole-volume corrected). This region has been associated in previous studies to self-distancing from negatively valenced pictures presented during the scan. The present study may provide evidence of the possible involvement of this brain area in spontaneously enacted self-distancing defensive strategies, which may be of relevance in resistant reactions in the course of a psychoanalytic psychotherapy.

**Keywords: psychoanalysis, fMRI, psychotherapy process Q-Set, single case studies, attachment**

## INTRODUCTION

The empirical investigation of the psychoanalytic process and outcome is of great importance to advance our knowledge of the psychoanalytic theory of treatment. Several studies have demonstrated the efficacy of long-term and short-term psychoanalytic treatment in randomized controlled trials (e.g., Gabbard et al., 2002; Leichsenring et al., 2004; Leichsenring and Rabung, 2008, 2011). Nevertheless, many clinicians and researchers argue that detailed single case studies, a time-honored instrument of psychoanalytic inquiry and knowledge dissemination (Donnellan, 1978; Edelson, 1985; Kächele et al., 2009) are still an essential complement to clinical trials in furthering our understanding of the psychoanalytic process and its relation to outcome (e.g., Kächele et al., 2006, 2009). Single case research has been often indicated as one of the most suitable approach for evaluating psychoanalytic treatments (Wallerstein and Sampson, 1971; Edelson, 1988; Hilliard, 1993). Recently, single case studies based on operationalized instruments have been developed in different domains (e.g., Kazdin, 1982). These efforts have produced psychotherapy studies focusing on computerized text-analytic measures (e.g., Mergenthaler and Kächele, 1996), process and outcome research (e.g., Hilliard, 1993; Orlinsky et al., 2004; Gullestad and Wilberg, 2011), and the combination of psychotherapy research and fMRI (Schiepek et al., 2009, 2013).

The aim of the present study was exploring for the first time the feasibility of single case research of an ongoing psychoanalysis in a neurobiological context using repeated fMRI measurements. We pursued the integration of clinical presentation, of operationalized formal instruments to describe the individual psychotherapeutic process, and of neuroimaging techniques to monitor the psychotherapeutic process on both the clinical and the neural levels. To this end, we collected functional neuroimaging data at monthly intervals from a patient undergoing psychoanalytic psychotherapy during exposure to attachment-relevant pictures (Buchheim et al., 2006, 2008). The main question we wanted to address was the extent to which the data from functional neuroimaging could be brought to bear on our theoretical understanding of the psychoanalytic process. Likewise, we were interested in verifying if existing interpretations of cortical activity gained in controlled experimental settings

from neuroimaging studies would maintain their explanatory power in the context of the single case study of a psychoanalytic process. A crucial issue was therefore the existence of an association between symptoms, the character of the relationship with the therapist in individual therapy hours, and variation in the signal from the attachment-relevant scenes probe in the scanner.

## MATERIALS AND METHODS

One year of psychoanalytic therapy of a patient with a chronic depressive disorder and narcissistic traits was assessed at monthly intervals ($N = 12$ sessions) with an established measure for the characterization of therapy (The Psychotherapy Process Q-Set, PQS; Jones, 2000), and with a functional neuroimaging probe that was successfully used to elicit signal in an adult attachment context in a previous study of the psychoanalytic treatment of recurrent depression (Buchheim et al., 2012).

The patient, a 42-years-old female lawyer, suffered from rapidly fluctuating affective states. Waking up the morning she knew that "this will be an easy day" or "this will be a difficult day." Her capacity for successful work and concentration was reduced when she felt depressed and in a "difficult day mood." During these occasions she isolated herself, tended to withdraw from relationships, and worked hard to hide her emotional vulnerability. This chronic and fluctuating depressive pathology and a fragile, vulnerable perception of self and others brought her in psychoanalytic treatment.

In order to obtain an objective assessment of the psychotherapy process describing the psychodynamic pattern of the patient and the interaction between the patient and the therapist, one session every 4 weeks (first session of the week) at regular intervals (compatible with interruptions due to vacations and illnesses) was audiotaped, transcribed, and analyzed with the PQS approach (12 sessions in all). The PQS (Jones, 2000; German version: Albani et al., 2007) is a rating instrument designed to provide a basic vocabulary for the description and classification of psychotherapy processes in a form suitable to quantitative analysis (Q-sort methodology). The PQS captures a wide range of events in the psychotherapeutic session attributable to both the therapist's activity and the patient, including transference manifestations, resistance, and the accompanying affective states.

Functional neuroimaging scans were taken on the same days as the recorded therapy hours. As in a previous study (Buchheim et al., 2012), attachment-relevant scenes were used to capture individual attachment-related features relevant for the psychotherapeutic relationship. In the scanner, the patient looked at the scenes used in a formal measure for the assessment of adult attachment representations (Adult Attachment Projective Picture System, AAP; Buchheim et al., 2006, 2008; George and West, 2012). These scenes were alternately accompanied by sentences neutrally describing their content, or by sentences that referred to the personally relevant content evoked by them as extracted by a previous AAP interview. The contrast of interest was the difference between the signal evoked by the personalized and the neutral textual descriptions of the scenes. This contrast detected neural substrates activated by the appraisal of the personal element in the attachment scenes, at the net of generic activations due to the perceptual encoding of the scenes and reading the textual description.

Note that we did not have access to changes in brain function during therapy, since the functional neuroimaging sessions necessarily took place after, and not during, therapy hours. However, we were aided in our attempt in establishing a link between mind states, therapy, and neural substrates by the oscillations of the patient between "difficult" and "easy" days, a change in mood that may have been relatively stable from the therapy hour to the functional neuroimaging session. Hence, the data we present document changes in these modes of emotional functioning that had consequences on the quality of the therapy hours, rather than the therapy hours themselves. The question of interest was the extent to which clinical data from the therapy hours and neural activation were reciprocally informative of the mental states at the base of the "easy" and "difficult" moods. This focus also allowed us to sidestep the issue of change over the course of therapy, which would possibly be confounded by habituation or learning effects in the neuroimaging data.

### PARTICIPANTS

The *analyst* was a very experienced training analyst with an interest in research. She agreed to take part in our study and to audiotape one therapy session a month for the PQS analysis. She works in a private practice as a psychiatrist.

The *patient* also agreed to take part in the study. She was given information about the study and signed a declaration of her willingness to participate for 1 year and to be assessed with several questionnaires and the functional neuroimaging scans. The treatment was paid by the health insurance. This study was approved by the ethical committee by the University of Ulm in the context of the Hanse-Neuro-Psychoanalysis Study (Buchheim et al., 2008, 2012). The patient gave written informed consent to the publication of the data. However, the case report should be written taking into consideration the need to protect the identity of the patient.

### TREATMENT

This patient was treated with a standard long-term psychoanalysis with a frequency of two face-to-face sessions per week. Standard key techniques included exploration, clarification, and interpretation. Interpretive interventions aimed to enhance the patient's insight into her repetitive conflicts sustaining her problems; supportive interventions aimed to strengthen abilities that were temporarily inaccessible to the patient's owing to acute stress (e.g., traumatic events) or were not sufficiently developed (e.g., Fonagy and Kächele, 2009; Shedler, 2010). The establishment of a helping (or therapeutic) alliance is regarded as an important component of supportive interventions. Transference, defined as the repetition of past experiences in present interpersonal relations, constitutes another important dimension of the therapeutic relationship. In psychodynamic psychotherapy, transference is regarded as a primary source of understanding and therapeutic change (e.g., Fonagy and Kächele, 2009). In this low frequency therapy, the analyst followed an intersubjective approach, characterized by the focus on the inner and outer reality of the patient's self and object representations and the aim to increase the patient's capacity to differentiate between reality and fantasy by enhancing

self-reflection (e.g., Ogden, 1977, 1989; Fonagy et al., 2004; Dreyer and Schmidt, 2008).

## CLINICAL AND BEHAVIORAL OUTCOME VARIABLES

The clinical and behavioral outcome data served different purposes. First, the monitoring of symptoms with self-rating scales documented changes in affective symptoms at the days of the data collection. In clinical studies, these data describe the level of symptoms and document changes during therapy (in the present case study, these measures indicated a substantially stable state over the year of the study, as detailed below). Second, the clinical rating of the hour by the therapist and the PQS documented the exchange between patient and analyst during therapy through the clinical impression and an operationalized assessment instrument. Variation in these data provided correlates to explore with the neuroimaging probe. Third, the AAP interview provided material on core attachment issues specific to the patient for the preparation of the stimuli used in the neuroimaging sessions. Almost as a side product, it also provided an assessment of the attachment pattern of this patient at the beginning of study. The AAP interview, however, is not administrable on a monthly basis and for this reason could not be used as a clinical correlate of the neuroimaging data in the present setting. Fourth, a post-scan self-rating questionnaire was administered to evaluate reported involvement with the stimuli presented during the scan session. These data were meant as an aid in interpreting the fMRI analysis. Finally, the results section also reports on the patient using a more customary clinical description informed by psychoanalytic views. We considered the clinical description an integral part of the results, this being a single case study. This description is meant to provide guidance on the psychopathology of this patient, to be compared with the functional role of neural structures identified in the neuroimaging study.

### *Clinical rating of the hour by the therapist*

The analyst rated on a clinical level dichotomously if the 12 sessions were "difficult" or "easy." According to her documentation the classification in "difficult" or "easy" was very clearly identifiable. The "difficult" sessions started with silence and remained quiet and inhibited. The "easy" sessions started fluently and remained talkative.

### *Psychopathology monitoring with self-rating scales*

At each scanning session, the patient filled a number of self-rating scales documenting her psychopathological state. State depressiveness was rated with the Collegium Internationale Psychiatriae Scalarum (CIPS)-depressiveness scale (Zerssen, 1976). This is a self-rating depressiveness scales provided in two parallel series of questions, which may be used in alternative turns in sequential assessments. The general burden of symptoms was gaged with the outcome questionnaire (OQ)-burden subscale (German version: Haug et al., 2004).

### *Psychotherapy process Q-set*

The PQS is an operationalized instrument for the characterization of therapy hours (Jones, 2000). It consists of 100 items covering a wide range of aspects in the behavior of the patient and her interaction with the therapist. Unlike most rating instruments, the items are not arranged in predefined groups that considered together provide scores on clinical dimensions identified *a priori*. Instead, a typical use of this instrument in psychotherapy research is the identification of hallmark of hours with specific characteristics. For example, one may attempt to identify items correlating with a negative therapeutic reaction, ascertained clinically in a carefully monitored therapy sample. Among their uses, these items can identify both the unity and coherence of treatment sessions, and detects changes between hours and patients. The PQS-instrument shows excellent inter-rater reliability, item reliability, concurrent, and predictive validity for several studies and various types of treatment samples (see Levy et al., 2012). The inter-rater reliability, assessed for all 100 items and tested by correlating the Q-sorts of multiple raters, is high as evidenced by levels of inter-rater agreement/reliability (kappa ranges from 0.83 to 0.89). Reliability varies from adequate to excellent for individual items, giving values between 0.50 and 0.95 (see Levy et al., 2012). In this study verbatim transcribed sessions were coded by two independent raters, who were blind to all therapy hours. Two independent trained judges rated all 12 psychotherapy sessions and achieved a correspondence of kappa between 0.80 and 0.97.

### *Statistical analysis of behavioral data*

Because of the inherently correlational and explorative character of data obtained with the PQS, we investigated the tendency of PQS scores to covary across items with a principal component analysis. To compute significance levels of principal components, we carried out 2000 Monte Carlo simulations in which principal component analyses were computed on data with the same item range and distribution, but varying independently from each other. Significance values were computed as quantiles of the first and second components of the simulations (to test the significance of the first and second component, respectively). Significant components provide evidence that a set of therapy characteristics occur together, suggesting the existence of recurrent interaction dynamics.

Hypothesis testing on PQS items were conducted on the linear trend (the months of therapy from 1 to 12) and on the classification of "easy" and "difficult" hours provided by the analyst. The first test documented the existence of a change in the tendency of these interaction dynamics to occur with different frequencies at the beginning and at the end of the period of the study. The second test constituted an objective verification of the clinical impression of the analyst. Tests were carried out independently on each PQS item, correcting for the multiple comparison using a permutation method with 2000 steps (Blair et al., 1994). In this approach, at each permutation the maximal (minimal) $t$-value obtained from conducting the test on the PQS item was recorded. The significance levels of high (low) $t$-values, with adjustment for multiple testing, were given by the quantiles of the recorded maximal (minimal) $t$-values.

### *Self-rating questionnaire after fMRI sessions*

To monitor the extent of emotional involvement and autobiographical character of the three core sentences during the course of the psychotherapy, we administered a self-rating questionnaire to the patient after each fMRI session. In the questionnaire the patient

was asked to rate the personalized sentences from the AAP scenes used in the scanner by answering the following two questions: "How much of the sentence applies to you autobiographically?" and "How strong did this sentence move you emotionally?" The patient had to assign a score between 1 and 7, where 1 meant not at all, 4 meant middle intensity, and 7 meant very much.

#### *AAP interview*

Attachment classification and fMRI-stimuli were derived from the AAP (George and West, 2012), an established and validated interview to assess attachment representations, based on a set of eight picture stimuli. The stimuli are line drawings of a neutral scene and seven attachment scenes (e.g., illness, separation, solitude, death, and threat). The AAP classification system designates the four main adult attachment groups identified using the AAI classification system (secure, dismissing, preoccupied, unresolved). Classifications are based on the rating of several scales (e.g., agency of self, connectedness, synchrony, deactivation) on the basis of verbatim transcripts of the stories to the seven attachment activating stimuli.

Administration involves asking participants in a semi-structured format to describe the scene in the picture, including what characters are thinking or feeling, and what they think might happen next. Three core sentences that represented the attachment pattern of the participants were extracted from the audiotaped responses to each AAP picture stimulus by two independent certified judges (e.g., "A girl is incarcerated in that big room," "My mother suffered until the end and the ambulance came often"). These sentences were paired to the respective picture to constitute the "personally relevant" trials tailored to each participant. These same pictures, paired to sentences describing only the environment of the depicted situation (e.g., "There is a window with curtains on the left and right," "There is a bed with a big blanket") constituted the "neutral" trials (see also Buchheim et al., 2012).

### NEUROIMAGING OUTCOME VARIABLES

The neuroimaging session took place on the same day as the recorded psychotherapy hour. It consisted of the task in the scanner and in the administration of a rating instrument to assess the patient's reaction to the items presented in the scanner.

#### *Neuroimaging task*

In each trial, the patient looked at pictures of attachment-relevant AAP scenes, accompanied by a short descriptive text. Each picture was presented for 20 s, followed by a fixation point for about the same duration (**Figure 1**). The AAP consists of a set of seven of such pictures; this set was repeated 12 times, for a total of 84 trials. Repetitions of the set were divided into two groups: those in which the descriptive text was a neutral rendering of the figures appearing in the scene (*neutral trials*), and those where the description was tailored to core conflicts of the patient as assessed in the initial AAP interview (*personally relevant trials*).

#### *Image acquisition*

MRI data were recorded using a 3-T Magnetom Allegra head scanner (Siemens, Erlangen, Germany), equipped with a standard head coil. In each session, 508 EPI $T_2$*-weighted whole brain volumes were acquired (TR/TE = 2500/30 ms, flip angle 90°, FOV 192 mm, matrix 64 × 64, voxel size 3 mm × 3 mm, slice thickness 3 mm, 44 slices, standard AC–PC orientation). Sessions were repeated in monthly intervals for a year, for a total of 12 sessions.

#### *Preprocessing and statistical analysis of neuroimaging data*

Data were analyzed with the Statistical Parametric Mapping (SPM) package (Frackowiak et al., 2003), using a voxelwise approach. After realignment and normalization into Montreal Neurological Institute (MNI) space, volumes were smoothed with a Gaussian isotropic kernel (8 mm full width-half maximum). The blood oxygenation level-dependent (BOLD) response function was modeled by convolving the trial onsets with a standard hemodynamic response function. Effects of interest were estimated for each session separately (in a model that included presentation of the scene + textual description combination and whether the combination was personalized or not) and brought to the second level to account for a random effect of sessions (Penny and Holmes, 2007). At the second level, main effects were tested with one-sample *t*-tests. The interaction between quality of the hour and personalized effect was given by an additional second-level regressor indicating whether the hour was "easy" or "difficult." This regressor is orthogonal to the one-sample *t*-test of the personalized effect (Viviani, 2010).

The main effect of interest of the study was given by the contrast personally relevant vs. neutral, and its interaction with the index of the quality of the session, as indicated by the therapist and its operational characterization through the PQS scores. To identify regions associated with the presentation of the personalized trials, we performed a whole-brain estimation of the model voxel by voxel. The significance levels reported in the text of section "Results" are corrected at cluster level (Poline and Mazoyer, 1993; Friston et al., 1994) for the whole volume.

The post-scan self-rating scales were analyzed separately from neuroimaging data using the freely available package R (The R Foundation for Statistical Computing, www.r-project.org, Vienna, Austria; repeated measures regression: function *lmer*, package lme4, version 2.13.1; Bates and Maechler, 2009). The dependent variable (emotional involvement or extent of autobiographical character of the scene–sentence couple) was modeled in a repeated measurements linear model as an effect of the hour character ("easy" or "difficult") and the personally relevant AAP scene as fixed effects, and the session and the sentences as grouping variables for the random effects.

## RESULTS

### CLINICAL DESCRIPTION OF THE PATIENT

The patient, a 42-years-old lawyer, suffered since the birth of her first daughter from rapidly fluctuating affective states. From a clinical point of view, the patients had a moderate functioning level. During the so-called "difficult day"-states she isolated herself and tended to withdraw herself in relationships and hide her emotional vulnerability in contrast to the so-called "easy days"-states, where the patient felt self-conscious and full of personal strength. Regarding her personality structure she showed some narcissistic features (Kernberg, 1984; Cain et al., 2008; Pincus and Lukowitsky, 2010), being self-centered and rather achievement oriented. She defined herself frequently via money, success,

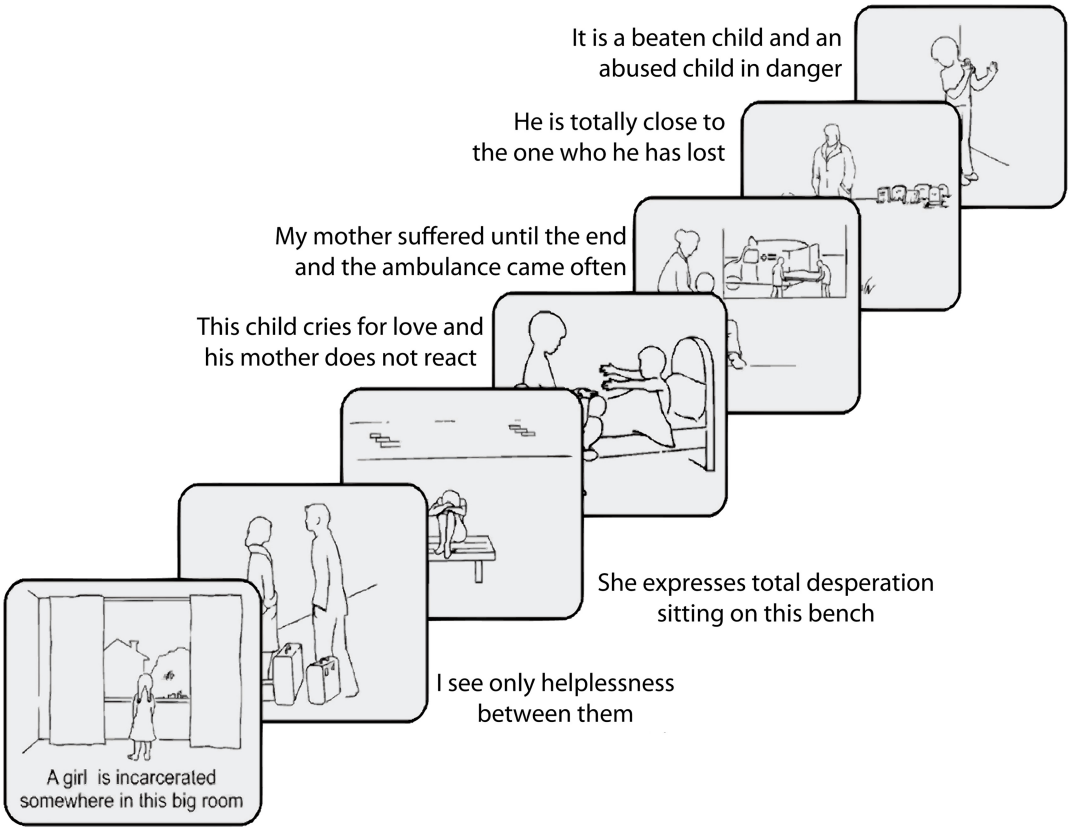


**FIGURE 1 | Schematic representation of the AAP scenes and sentences used in the functional neuroimaging study (example of a personalized trial).**

and reputation. When she felt in her job that clients were not as satisfied with her work as she expected from herself she broke down and was ruminating anxiously if they will come back. This pattern demonstrated that her self-esteem fluctuated according to the gratifying or frustrating experiences in relationships and how she evaluated the distance between the goals and aspirations. Because of her harsh super-ego demand for perfection she was in an instable inner state and self-esteem could be diminished rapidly.

The patient lived in a long-lasting relationship. However, she characterized the relationship with her husband as competitive with respect to their tendency to experience rivalry and envy. Moreover, there was a clear discrepancy between her self-perception and the perception that significant others had of the patient. Although easier days were subjectively felt more pleasant by the patient, her husband reportedly found it very difficult to deal with her. This often led to constant, seemingly unsolvable conflicts and to repeatedly considering separation.

One of her major unconscious defensive structure seemed to circle around fantasies of success and grandiosity, leading to her dependency to be admired by others and to bouts of insecurity disrupting her sense of grandiosity or specialness (for a description of the related dynamic, see Kernberg and Yeomans, 2013).

According to the observations of the analyst collected over 1 year of clinical work, the following topics may be considered key to the psychodynamic understanding of the patient and her treatment:

1. On "difficult" days the patient showed a severely inhibited capacity to think and to express feelings and thoughts and fell into silence. On "easy" days the patient talked expansively and her personality appeared strong.
2. The association of the fluctuating symptoms with unresolved loss experiences and fear due to uncontrollable guilt-feelings.

As we shall see later, these two core issues could be retrieved in the formal assessment of the interaction between the patient and the therapist using the PQS methodology.

From a psychodynamic and biographic perspective the analyst suggested that two events of death were useful to understand the nature of the patient's symptoms. These events revealed the underlying vulnerability of the patient with respect to this issue and the related latent feelings of helplessness and impotence. When the patient was 30-years old her mother died unexpectedly. She felt guilty, because she was unable to call the emergency doctor in time. Moreover, the tragic loss through death of a colleague some years previously coincided with the birth of her first child, a son. Again the patient felt guilty, because she was not able to reach her colleague in time to be able to help her. Her fluctuating depressive symptoms might be interpreted as the outcome of this defensive structure. On "easy days" her functioning was predominantly

characterized by externalization with an increase of activity and personal strength, while on "difficult days" internalization led to inhibition of activity and severe self-doubts. These latter phases were characterized by affective distance between the patient and her object world in an effort to preserve the illusion of control relative to object loss (Modell, 1975).

Since the patient demonstrated a complex chronic affective disorder with difficult personality traits and a rigid defensive structure, there was an indication for long-term psychoanalytic treatment with two sessions per week (Leichsenring and Rabung, 2011). The treatment setting was face-to-face, thus creating a positive stable counterpole to her mood changes. The positive stabilizing effect of the therapy was noticeable early in the treatment even though the total process was taking a very long time. The treatment centered on the deeper understanding of her uncontrollable mood-shifts and her impaired self-perception and perception of others. The question of failure and/or the continuing of the analytic work were constantly present. The transference relationship was mirrored by her experiences of loss: she failed to prevent the unexpected deaths, and for a long time the analyst and the patient failed to prevent the unexpected mood-shifts and to find ways how she could regulate and stabilize her affective instability. Gradually, the patients internalized a better perception of herself and it became easier for the patient to succeed regulating her mood toward the state characterizing "easy" days. One major focus of the treatment was to increase the patient's ability to react timely in case of severe events like illness or death, and therefore to be able to process these potential traumatic events in a more controlled and integrated way.

### ATTACHMENT DATA

The patient was administered the AAP interview at the beginning of the fMRI experiments and 1 year later. The AAP interview had two purposes. On the one hand we assessed the patient's attachment representation at the beginning of the fMRI assessment and on the other hand we extracted core sentences of the patient's narratives in the AAP interview as the personalized stimulus material in the fMRI setting (see Section "Neuroimaging Task"). The patient was classified as unresolved (i.e., disorganized). Unresolved stories typically leave characters without protection, describe feelings of extreme mental distress that have not been diminished or transformed, or leave threatening images looming without addressing them further. The patient demonstrated a lack of resolution especially in the AAP Picture "Cemetery" where the loss of the father was associated with mourning, loneliness and a present dialogue with the dead father, which indicated a spectral quality.

### ANALYSIS OF SELF-RATING SCALES

Analysis of the CIPS-depressiveness score gave a mean value of 12.2 (SD 5.2, range 8–19), indicating affective symptoms of moderate intensity. The regression of the scores over time failed to demonstrate the existence of changes. Nominally, in the examined monthly sessions the patient became more depressed during the year she was monitored (**Figure 2**), but the result was far from significant ($t = 1.05$; df $= 10$, $p = 0.34$, two-tailed).

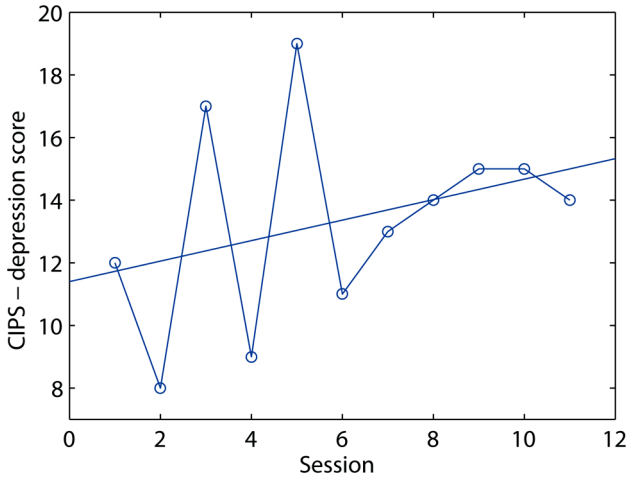


**FIGURE 2 | Plot of depressiveness scores (*y*-axis) over the 12 months of the study (*x*-axis).**

The general burden of symptom, as measured by the OQ subscale, was on average 41.75 (SD 5.0, range 33.53), indicating alternating degree of symptom severities crossing the line of norm values (Haug et al., 2004). Like depressiveness, the symptom burden also increased lightly, but not significantly, during this period ($t = 1.16$, df $= 10$, $p = 0.27$, two-tailed).

### PQS SCORES

The analysis of the PQS scores took place in three steps. In the first step, we undertook an explorative analysis to answer the question of whether there were consistent changes over therapy hours across different items of the PQS, by carrying out a principal component analysis of the PQS scores. This analysis aimed at detecting items that were high or low together in the same hour, without imposing *a priori* constraints on what these items should be, as would be the case if items had been grouped into preformed scores. We also looked at whether these changes were consistent with a linear trend (i.e., a gradual change over time). In the second step, we looked at the existence of items that were associated with the analyst's classification of the hours in good and bad. In the final step, we looked at whether changes detected during the explorative analysis related to the changes associated with the analyst's judgment.

In the principal component analysis of PQS scores, the first detected component, which explained about 32% of the variance of PQS items over time, was highly significant ($p < 0.001$). A second component only reached trend significance ($p = 0.06$), explaining 16.7% of the overall variance over time. Further components, explaining 13% of the variance of less, failed to reach significance even at trend level. The 10 items scoring highest in the first and second components are shown in **Table 1**.

Several items in the principal component analysis scored negative values. The PQS manual contains specific indications to score items as distinctively low. In the first component, a low score on item 54 is given for rambling or incoherent communications, and on item 23 for lack of a guiding discourse thread; on item 13 for the patients appearing bored or dull, and on item 74 grave or somber.

**Table 1 | Ten highest scoring items from the principal component analysis of the PQS.**

| Polarity | Weight | PQS item |
|---|---|---|
| **First component** | | |
| + | 0.41 | 25: Patient has difficulty beginning the hour. |
| + | 0.33 | 12: Silences occur during the hour. |
| − | −0.30 | 54: Patient is clear and organized in self-expression. |
| + | 0.25 | 7: Patient is anxious or tense (vs. calm and relaxed). |
| − | −0.21 | 13: Patient is animated or excited. |
| − | −0.21 | 23: Dialog has a specific focus. |
| − | −0.20 | 74: Humor is used. |
| + | 0.16 | 8: Patient is concerned or conflicted about his or her dependence on the therapist (vs. comfortable with dependency, or wanting dependency). |
| − | −0.16 | 87: Patient is controlling. |
| + | 0.15 | 15: Patient does not initiate or elaborate topics. |
| **Second component** | | |
| − | −0.29 | 30: Discussion centers on cognitive themes, i.e., about ideas or belief systems. |
| − | −0.28 | 31: Therapist asks for more information or elaboration. |
| + | 0.27 | 40: Therapist makes interpretations referring to actual people in the patient's life. |
| − | −0.25 | 45: Therapist adopts supportive stance. |
| + | 0.25 | 63: Patient's interpersonal relationships are a major theme. |
| − | −0.22 | 12: Silences occur during the hour. |
| − | −0.21 | 66: Therapist is directly reassuring |
| − | −0.20 | 95: Patient feels helped. |
| + | 0.19 | 1: Patient verbalizes negative feelings (e.g., criticism, hostility) toward therapist (vs. makes approving or admiring remarks). |
| + | 0.19 | 49: The patient experiences ambivalent or conflicted feelings about the therapist. |

Considered together with items with high scores (whose interpretation is immediate), they show that component one prevalently collected items suggesting difficult or inhibited communication of the patient toward the analyst, with frequent phases of silence. These occurred together with other items suggesting the presence of a tense, sober mood (items 7, 13, 74).

The second component appears to characterize form and content of the intervention of the analyst (items 31, 40, 45, 63, 66) and the sometimes difficult reaction of the patient to them (items 1, 49, 95).

We then tested the existence of a linear trend in the changes over time in these component scores. This would have been the case, for example, if the character of the hours changed over the year of therapy, and these components reflected this systematic change. However, the regression of the component scores on the time trend was not significant (first component: $t = 0.99$, $\mathrm{df} = 9$, $p = 0.35$, two-tailed; second component: $t = 0.82$, $\mathrm{df} = 9$, $p = 0.43$, two-tailed), suggesting that they did not change over time (**Figure 3**). Even if the main components did not appear to reflect a change over time, it is conceivable that some other isolated item did. To verify this hypothesis, we tested the regression of each item score over time separately, correcting the significance level for the 100 tests. Also this analysis failed to detect items reflecting a change over the year of therapy. The item that was most associated with time was item 76 ("Therapist suggests that patient accept responsibility for his or her problems," which however failed to reach significance ($t = 4.22$, $p = 0.14$, two-tailed corrected for multiple comparisons). In summary, change over time in the PQS scores did not document a systematic change after 1 year of therapy relative to the beginning of the monitoring period.

In the second step of the analysis we looked at the existence of items that were associated with the analyst's classification of the hours in "easy" and "difficult." Both easy and difficult hours occurred during this year, and a logistic regression of the occurrence of easy hours over time showed the absence of a significant time trend ($z = -0.53$, $p = 0.60$). The separate regression of each PQS item on the analyst indicator of the quality of the hour detected three significant items, after correcting significance levels for multiple comparisons: item 12 ("Silences occur during the hour"), $t = -9.16$, $p = 0.004$ (two-tailed, corrected); item 61 ("Patient feels shy and embarrassed (vs. un-self-conscious and assured.)," $t = -5.76$, $p = 0.03$; item 54 ("Patient is clear and organized in self-expression"), $t = 5.39$, $p = 0.04$. A fourth item reached trend significance, item 7 ("Patient is anxious or tense (vs. calm and relaxed)."), $t = -4.95$, $p = 0.063$.

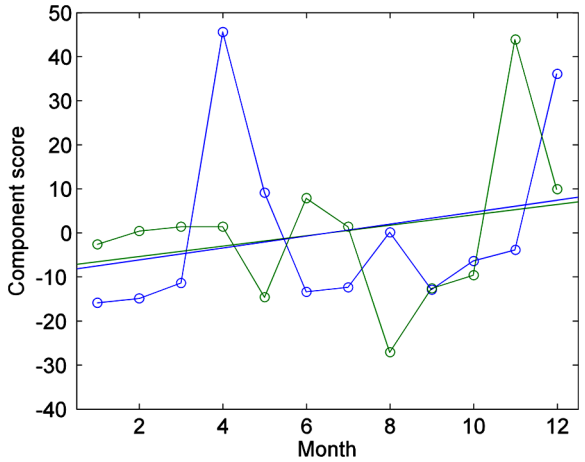


**FIGURE 3 | Plot of first component scores over time, together with the respective linear trends (on the *x*-axis by the monthly session).** In blue, first component scores; in green, second component scores. Both component scores display a small tendency to increase over time, which however was not significant.

Finally, we looked at whether changes detected during the explorative principal component analysis in the form of component scores related to the changes associated with the analyst's judgment. There was a significant association between the first component scores and the analyst's indicator of the quality of the hour ($t = -5.03$, df $= 9$, $p = 0.0006$). The second component, in contrast, was not significantly associated ($t = 1.01$, df $= 9$, $p = 0.33$).

In summary, there was at least one set of PQS items that changed together across therapy hours. These changes were not associated with a time trend, indicating stability of the underlying psychotherapy pattern; however, they were associated with the occurrence of "easy" and "difficult" days. This result did not change if the PQS items were regressed individually on time and day difficulty.

### CORE PSYCHODYNAMIC FEATURES OF THE PATIENT AND PQS RESULTS: AN EXPLORATORY COMPARISON

We compared the clinical features of "difficult" and "easy" days with the first component from the PQS, obtained independently from information on the day difficulty (see **Table 2**). This comparison revealed convergent patterns. The clinical description of the analyst, emphasizing the difficulties of expression of the patient, is consistent with the items in the first component detailing inhibited communication, silence, or ineffective content on difficult days. The identification by the analyst of unresolved feelings of loss corresponds to the items related to tense and sober mood. We conclude that the PQS analysis could validate the subjective evaluations of the analyst.

### ANALYSIS OF POST-SCAN SELF-RATING QUESTIONNAIRE

The patient was asked after each fMRI session to rate personalized sentences from the fMRI task with respect of self-involvement and autobiographical content (see Section "Materials and Methods"). The analysis of emotional self-involvement revealed that the rating was on the whole significantly higher in the fMRI sessions that followed "easy" therapy hours ($t = 2.08$, df $= 9$, $p = 0.03$, one-tailed). This result did not change if the autobiographical rating was added as a confounding covariate to the model ($t = 2.08$). This expanded model also revealed that the autobiographical rating was in the individual items associated with the level of emotional involvement rating ($t = 3.9$, df $= 193$, $p < 0.001$). In contrast, there was no significant change in ratings of the autobiographical character of the personalized sentences in association of the quality of the hour ($t = 1.27$, df $= 9$, $p = 0.12$ one-tailed).

In summary, these self-rating data confirmed the existence of a qualitative difference between "easy" and "difficult" days that involved the stimuli presented in the scanner through the tendency of a higher self-rated emotional involvement on "easy" days. However, over and above this association, there was an even stronger association at each individual rating between the level of self-involvement and the level of autobiographical character of the scene + text combination.

### NEUROIMAGING RESULTS

When viewing the pictures described by personalized text, relative to those with neutral descriptions, the patient activated several areas, prevalently on the left. The most prominent activations involved the ventrolateral and the dorsolateral prefrontal cortex, the perigenual portion of the medial prefrontal cortex, the posterior cingulate and precuneus, the middle temporal gyrus, and the anterior tip of the inferior temporal gyrus, and the occipital/calcarine cortex (see **Figure 4A** and **Table 3**). No area was significantly more active when looking at the neutral scenes.

The interaction of the effect of personal relevance with goodness of therapy hours was significant in the posterior cingulate/precuneal region (MNI coordinates, *x*, *y*, *z*: $-6$, $-60$, 40, $t = 6.7$, cluster size in voxels: 633, $p = 0.017$). Here, the signal while looking at personalized scenes was higher when the therapy hour was bad. This area, shown in **Figure 1B**, was part of the medial prefrontal network that was associated with viewing personalized scenes (**Figure 1A**). Other, smaller areas detected in the interaction failed to reach significance. No significant interaction was observed in the opposite direction.

We also tested the interaction between the effect of personal relevance and a linear time trend, to detect changes in activation that developed during the year of therapy. In the interaction with the positive time trend, a cluster extending from the left postcentral gyrus to the middle frontal gyrus was significant (MNI coordinates, *x*, *y*, *z*: $-54$, $-12$, 40, $t = 10.2$, cluster size in voxels: 1410, $p < 0.001$). This interaction partially overlapped with the prefrontal interaction in **Figure 4A** (d, dorsolateral prefrontal cortex). No effect was observed in the interaction with a negative time trend.

## DISCUSSION

Recently, the issue of the relationship between Freudian thought or psychoanalytic theory and technique more generally and neuroscience has been the object of renewed interest (Carhart-Harris et al., 2008; Carhart-Harris and Friston, 2010; Solms and Panksepp, 2012; Zellner, 2012; Schmeing et al., 2013). In the present study, we attempted to integrate a clinical description of

**Table 2 | Clinical characteristics compared to PQS-items (principal component analysis).**

| Clinical characteristics | PQS-items |
|---|---|
| On "difficult" days the patient showed a severely inhibited capacity to think and to express feelings and thoughts and fell in silence. | Item 25: Patient has difficulty beginning the hour.<br>Item 12: Silences occur during the hour. 15: Patient does not initiate or elaborate topics.<br>Item 15: Patient does not initiate or elaborate topics. |
| The association of the fluctuating symptoms with unresolved loss experiences and fear due to uncontrollable guilt-feelings | Item 7: Patient is anxious or tense (vs. calm and relaxed).<br>Item 8: Patient is concerned or conflicted about his or her dependence on the therapist (vs. comfortable with dependency, or wanting dependency). |

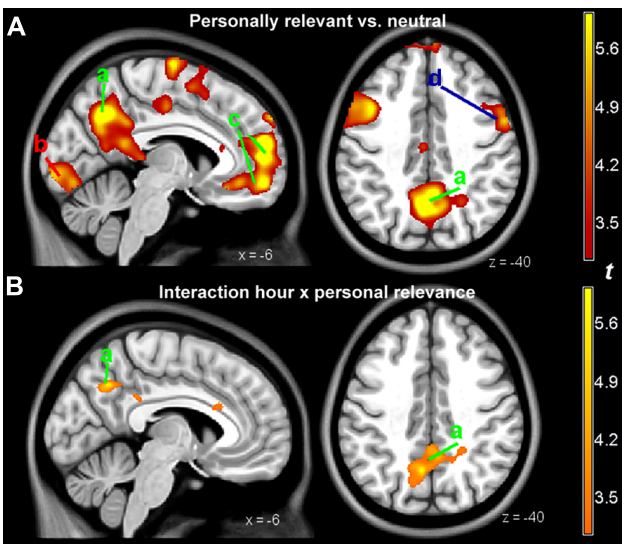


**FIGURE 4 | (A)** Parametric maps of activations detected in the personally relevant vs. neutral contrast, overlaid on a template image. **(B)** Parametric maps of the interaction of the same contrast with hour quality, as rated by the therapist. Slices positioned at MNI coordinates $x = -6$ (left) and $z = 40$ (right). For illustration purposes, the parametric map was thresholded at $p < 0.005$, uncorrected, and a cluster size of 150 voxels (1.2 $cm^3$). a, precuneus and posterior cingulate, active at both the contrast personally relevant vs. neutral and its interaction with hour quality; b, calcarine cortex; c, perigenual medial prefrontal cortex; d, dorsolateral prefrontal cortex. Areas a and c (labeled in green) belong to the "default network system"; area d to the dorsal attentional network (in blue). The red label b refers to primary visual areas.

the psychoanalytic process with two empirical instruments, one providing an operationalized assessment of the therapeutic interaction, and the other information on brain activity based on a functional neuroimaging probe. Our aim was to explore the extent to which the two main mental states of the patient and their effect on the psychoanalytic interaction could be observed not only at the clinical level, but also through the data delivered by these two additional instruments.

Analysis of the symptomatic scales gave the picture of a patient with affective symptom severity of moderate intensity, occurring in a patient with a personality with narcissistic features, as described in detail in Section "Results." The unresolved attachment pattern emerging from the AAP interview is consistent with the analyst's clinical presentation and with recent attachment data on patients, comorbid with borderline personality disorder and narcissistic personality disorder (Diamond et al., 2012).

The analysis of the PQS data showed that sessions differed along a main axis, defined by the first component. This component was highly correlated with the judgment of the analyst on the quality of the sessions. This analysis revealed that "easy" hours were associated with items describing the deeper understanding of relationship issues, "difficult" hours with silence in the therapy hours and difficulties of the patient to feel at ease. Furthermore, there was no evidence in the PQS data of a linear trend over time that reflected systematic changes from the initial to the final phases of the year monitored by the study. In summary, the main change across sessions present in the PQS data was the one documented by the analyst through her judgment in a phase of therapy where the patient remained stable. This source of change was not associated with a time trend, as "easy" or "difficult" days did not occur more often at the beginning or end of the observation year. This allows excluding the confounds of habituation or learning effects from the regressor representing quality of the hour.

The activation pattern in the contrast of the main effect personally relevant vs. neutral (**Figure 4A**) was characterized by the presence of two main groups of areas. The first included areas that are often active in functional neuroimaging studies and that are known to be active while carrying out a focused task (Duncan and Owen, 2000). This group includes the ventrolateral and the dorsolateral prefrontal cortex, and the occipital/calcarine cortex (for visually presented stimuli). The second group may be considered more specific for the material used in the present study, and included areas in the medial wall (anterior cingulate, and the posterior cingulate and precuneus). The activation pattern of these areas was consistent with the activation found in studies in the literature in which participants were asked to judge the degree to which stimuli presented during the scan were attributed to the self, or were felt to be part on oneself/one's own description (**Figure 5**; for a systematic review and meta-analysis of the literature, see van der Meer et al., 2010; Qin and Northoff, 2011). The medial prefrontal cortex may also be associated with changes after the therapy of affective disorders (Messina et al., 2013). We therefore considered the areas in this second group as those most likely involved in processing the personally relevant content of the stimuli.

**Table 3 | Activations for the contrast personalized vs. neutral.**

| MNI coord. (mm) | Brodmann area | peak *t* | *p* (peak lev.) | *k* | *p* (cl. lev.) |
|---|---|---|---|---|---|
| −50 30 −2 | L Inf. frontal orb. (BA45) | 13.84 | 0.001 | 10393 | <0.001 |
| −46 −2 −46 | L Inf. temporal (BA20) | 11.67 | 0.007 | s.c. | |
| −68 −52 8 | L Mid. temporal (BA21) | 10.67 | 0.020 | s.c. | |
| −8 56 20 | L Med. Sup. frontal (BA10) | 8.38 | 0.148 | 3131 | <0.001 |
| −6 56 8 | L Med. Sup. frontal (BA10) | 8.03 | 0.197 | s.c. | |
| −12 36 −8 | L Mid. frontal orb. (BA11) | 7.01 | 0.440 | s.c. | |
| 22 −100 10 | R Sup. occipital (BA17) | 7.84 | 0.230 | 2787 | <0.001 |
| 8 −86 0 | R calcarine (BA17) | 7.43 | 0.319 | s.c. | |
| 20 −88 2 | R calcarine (BA18) | 6.62 | 0.575 | s.c. | |
| −4 −10 76 | L Suppl. motor area (BA6) | 6.48 | 0.627 | 834 | 0.002 |
| −4 2 58 | L Suppl. motor area (BA6) | 4.58 | 0.999 | s.c. | |
| −12 8 74 | L Sup. frontal (BA6) | 4.22 | 1.000 | s.c. | |
| 54 −6 52 | R Precentral (BA6) | 5.65 | 0.904 | 800 | 0.002 |
| 54 4 38 | R Precentral (BA6) | 5.52 | 0.932 | s.c. | |
| 42 14 30 | R Inf. frontal Operc. (BA48) | 4.91 | 0.995 | s.c. | |
| 68 −36 −2 | R Mid. temporal (BA21) | 5.22 | 0.976 | 245 | 0.372 |
| 62 −34 10 | R Sup. temporal (BA22) | 4.63 | 0.999 | s.c. | |
| 66 −42 20 | R Sup. temporal (BA22) | 4.49 | 1.000 | s.c. | |
| −4 −14 44 | L Mid. cingulum (BA23) | 5.19 | 0.979 | 199 | 0.561 |
| −10 −20 50 | L Mid. cingulum (BA23) | 3.95 | 1.000 | s.c. | |
| −40 −46 56 | L Inf. parietal (BA40) | 5.08 | 0.987 | 173 | 0.686 |

*Shown are peaks at least 8 mm apart from clusters of at least 150 voxels (1.2 $cm^3$), and uncorrected significance $p < 0.005$. Explanation of abbreviations: MNI coord. (mm.), Montreal Neurological Institute coordinates (in millimeters); p (peak lev.), significance level, peak correction according to random field theory; k, cluster size, in 2 × 2 × 2 mm. voxels; p (cl. lev.): significance level, cluster correction according to random field theory; s.c., same cluster; L, left; R, right; Inf., inferior; Mid., middle; Med., medial; Sup., superior; Orb., orbital; Suppl., supplementary; Operc., operculum.*

Within this pattern of activation of areas associated to the self and personal relevance, the posterior cingulate cortex was modulated by the interaction with the quality of the therapy hours that had immediately preceded the scan. This association represent evidence of a neural substrates accompanying opposing mental states that, as shown in the self-rating scales, the judgment of the analyst on the quality of the hour, and the formal instrument for assessing the therapeutic exchange, represented a coherent constellation of internally experienced and interpersonally exchanged affect.

The posterior cingulate cortex has been shown in other studies to be modulated by self-distancing from negatively valenced pictures presented during the scan (Koenigsberg et al., 2010) or when down-regulating the reaction to a negative stimulus by self-distraction (Kanske et al., 2011). Of particular interest in the present context is the study by van Reekum et al. (2007), in which gaze fixations were recorded while participants viewed aversive scenes and were left free to choose the down-regulating strategy. This area highly correlated with the amount of eye movements of the participants, who were directing their gaze so as to avoid the focal area of the image where the disturbing content was represented. This area was also reported to be active in regulation strategies adopted by patients with personality disorders characterized by poor emotion regulation (Koenigsberg et al., 2009; Doering et al., 2012; Lang et al., 2012).

The self-rating data collected after the scan confirmed the association between the enactment of a self-distancing strategy from the material and the quality of the hour. On "difficult" days, the patient indicated that her overall emotional involvement with the visuotextual material was lower than on the "easy" days. This corresponded to a higher activity in the posterior cingulate area, associated in the previous studies with self-distancing emotion regulation strategies. In view of the documented association between the quality of the hour and the quality of the interaction with the therapist, and the clinical judgment of the therapist himself, the present study provides evidence on the possible involvement of the posterior cingulate area in spontaneously enacted self-distancing emotion-handling strategies representing defensive maneuvers in the course of a psychoanalytic therapy.

Among the areas active in the contrast personally relevant vs. neutral there were also areas prevalently involved in attentional processes (dorsolateral prefrontal cortex; **Figure 4A** letter c). Also this area was modulated during the year of therapy, showing a progressive increase of the signal due to personally relevant trials. This suggests a dissociation of the areas detected in the contrast

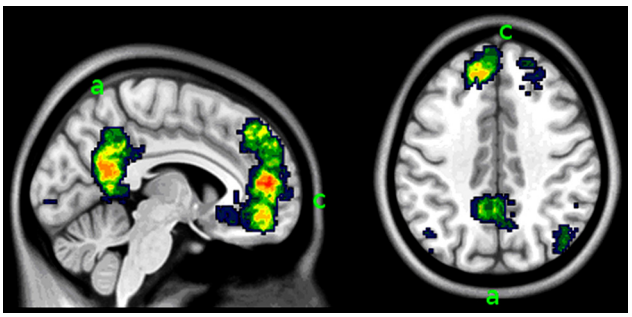


**FIGURE 5 | Areas in the medial face of the brain associated with self-representation.** This image synthesizes data in the neuroimaging literature of studies concerned with self-referentiality using automated keyword search and meta-analytic methods (from www.neurosynth.org, search key "self-referential"; Yarkoni et al., 2011). Slices positioned at MNI coordinates $x = -6$ (left) and $z = 40$ (right). The comparison with the activation detected in the study in the contrast personally relevant vs. neutral contrast (**Figure 4**) shows correspondence of activation in the areas in the medial aspect of the brain: the precuneus and posterior cingulate (a) and the perigenual medial prefrontal cortex (c).

personally relevant vs. neutral, with the posterior medial area associating with quality of the hour, and the dorsolateral prefrontal areas associating with change over time. The change over time in the dorsolateral prefrontal cortex might be due to a progressive loss of attentional pull of the non-relevant trials, or to the increased recruitment of attentional resources in looking at scenes in the personally relevant trials. From a clinical point of view it could mean that the patient was more effective in appraising and reflecting on her own personal core attachment-related issues.

There are several noteworthy limitations of this study. First, treatment did not follow a manualized psychoanalytic psychotherapy. However, it was conducted by adhering to specific core techniques, as described in section "Materials and Methods," by a very experienced psychoanalyst. Second, in the attachment paradigm used in the scanner no pictures without attachment content were present. This is consistent with the choice to investigate personal relevance in the context of material likely to evoke core emotional issues, as in previous work (Buchheim et al., 2012). Future work will have to address the issue of the neural response to attachment pictures of the kind used in the AAP in comparison with neutral pictures of similar content and complexity, but differing attachment relevance and interpersonal quality or emotionality, and its capacity to capture affective psychopathology. Third, the fluctuation between two cognitive–emotional states (easy and difficult days, easy and difficult sessions) may have been indicative of pattern transitions that may be analyzed with approaches focusing on self-organization and non-linear dynamics in psychotherapy (see e.g., Boston Change Process Study Group, 2005; Schiepek et al., 2009, 2013). However, this aspect of the psychotherapeutic interaction fell outside of the scope of the present study.

In summary, this case report gives indications on the interplay between activity in neural circuits and quality of the psychotherapeutic sessions in the context of psychoanalytic process research. In this specific single case, major characteristics of the patient's defensive structure could be demonstrated on a behavioral and neural level and validated the subjective evaluation of the analyst. Specifically, affective distancing has been identified in the literature as a hallmark defensive maneuver in personality organization with narcissistic traits (Modell, 1975). Using functional neuroimaging, we were able to objectify the defensive structure of this patient during this phase of psychoanalytic treatment and the occurrence of difficult sessions.

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# Neural activity during free association to conflict-related sentences

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Psychodynamic conflicts form an important construct to understand the genesis and maintenance of mental disorders. Conflict-related themes should therefore provoke strong reactions on the behavioral, physiological, and neural level. We confronted $N = 18$ healthy subjects with a vast array of sentences describing typical psychodynamic conflict themes in the fMRI scanner and let them associate spontaneously in reaction. The overt associations were then analyzed according to psychoanalytic theory and the system of operationalized psychodynamic diagnosis and used as a genuinely psychodynamic indicator, whether each potentially conflict-related sentence actually touched a conflict theme of the individual. Behavioral, physiological, and neural reactions were compared between those subjects with an "apparent conflict" and those with "absent conflicts." The first group reported stronger agreement with the conflict-related sentences, more negative valence in reaction, had higher levels of skin conductance reactivity and exhibited stronger activation in the anterior cingulate cortex, amongst other functions involved in emotion processing and conflict-monitoring. In conjunction, we interpret this activity as a possible correlate of subjects' inherent reactions and regulatory processes evoked by conflict themes. This study makes a point for the fruitfulness of the neuropsychoanalytic endeavor by using free association, the classical technique most commonly used in psychoanalysis, to investigate aspects of conflict processing in neuroimaging.

**Keywords: neuropsychoanalysis, psychoanalysis, neuroscience, free association, fMRI, operationalized psychodynamic diagnostics, emotion processing**

## INTRODUCTION

This study is a contribution in the field of neuropsychoanalysis. The term itself was coined in 1999 with the inauguration of the respective journal and can broadly be defined as the attempt to bridge psychoanalysis and neuroscience on multiple layers. Pioneers in the field started with investigations of patients with focal brain damage with techniques derived from psychoanalysis (Kaplan-Solms and Solms, 2000). Later on, studies were concerned with the investigation of phenomena described by psychoanalysis (e.g., repression, dreams) with neuroscientific methods (Solms and Turnbull, 2011). Many books and reviews have been written that cover theoretical as well as empirical aspects of this new scientific field (Solms and Turnbull, 2002; Fotopoulou et al., 2012; Panksepp and Solms, 2012). This is a broad new field with studies ranging from psychoanalytic observations in patients with brain lesions (Kaplan-Solms and Solms, 2000) to investigations on the neural changes during psychoanalysis (Buchheim et al., 2012). A comprehensive review of the empirical work in neuropsychoanalysis is provided by Sauvagnat et al. (2010). This work includes operationalizations of specific psychoanalytic concepts such as, e.g., dreams (Ruby, 2011), repression (Erdelyi, 2006), and primary-process thinking (Carhart-Harris and Friston, 2010).

In this study, we focus on an approach that has been termed "psychoanalytically informed neuroscience" – i.e., the testing of concepts associated with psychoanalysis with neuroscientific methods (Solms and Turnbull, 2011). This study investigates the concept of "psychodynamic conflict" using the (originally therapeutic) method of free association to potentially conflict-related contents inside the fMRI scanner. Being a major component of psychoanalytic theory and practice, psychodynamic conflicts represent a powerful construct that helps understanding mental disorders, their genesis and eventual "maintenance" (Person et al., 2005). Different biographical experiences may lead to the formation of psychodynamic conflicts, which consist of a main theme (e.g., the tension between the desire for autonomy and the need for dependency, or difficulties to adequately value one's self-esteem). Such conflicts comprise of typical core affects, modes of transference and counter-transference, and span wide areas of the subject's life (family, friends, job, recreational, etc.). Hence, if a theme comprised in the subject's conflict is touched in a real-life situation, reactions on the behavioral, cognitive, and physiological level should be expected, that call for the regulation of cognitions, impulses and, most importantly, emotions. Such regulatory processes can show varying degrees of consciousness depending on the conflict and subjects' conscious coping with it (Brenner, 1982; Mentzos, 1984). The regulatory coping

with conflict-related themes is well-understood in clinical contexts (Person et al., 2005) and guides many psychodynamic forms of psychotherapy (Strupp and Binder, 1985; Wöller and Kruse, 2010). The neural correlates of such processes have not been studied, though. Therefore, in this pilot study, we searched for neural and psychophysiological activation when subjects have to deal with conflict-related themes. In an economic first approach, we presented healthy subjects with a wide array of sentences depicting multiple potentially conflict-related themes and used their spontaneous associations to them as a genuinely psychodynamic indicator of whether the sentences actually touched a conflict-theme or not. Behavioral, psychophysiological, and neural reactions in only those subjects where an actual conflict is touched could then be a correlate of their subjective reactions to the conflict-related content or any regulatory processes mentioned above. In detail, we exposed healthy individuals sequentially to three different types of sentences in the MRI scanner and let them associate spontaneously what came into their minds after reading each sentence. The three conditions were neutral, unspecific negative emotional, and sentences that were also negative emotional but constructed in a psychoanalytically informed way to reflect possible psychodynamic conflicts. Part of the data obtained in this study has already been published (Schmeing et al., 2013) and showed that conflict-related sentences in general (i.e., irrespective of actual relevance for the subjects), among other effects, led to higher skin conductance reactivity (SCR) and enhanced activation of the anterior cingulate cortex/pre-supplementary motor area (ACC/pre-SMA) in the whole group of healthy subjects. Both effects could well be interpreted as being a correlate of subjects' affective reactions and emotional processing. To increase specificity of results, though, the individual impact a given stimulus has on the subject has to be taken into account (Kessler et al., 2011a,b). As conflict-related sentences were constructed on a theoretical basis (psychoanalysis) reflecting common themes of autonomy/dependency and self-esteem, they were the same for all subjects. To disentangle the actual impact of the sentences, expert psychotherapists trained in psychoanalysis assessed the audio-taped free association to the conflict-related sentences of subjects post-hoc, based on their clinical experience and descriptions of manifestations of common psychodynamic conflicts as provided by the Operationalized Psychodynamic Diagnostics Manual (OPD-Task-Force, 2008). The guiding questions were: does this sentence actually touch a conflict theme apparent in the subject? Is it of relevance because the subject struggles with this theme, whether consciously or unconsciously? This analysis led to a separation of tested subjects into two groups: "apparent conflict" comprised individuals with at least one of the associations reflecting a possible psychodynamic conflict; "absent conflict" consisted of individuals who did not show signs of conflict in any of their associations. Details of the rating process can be found in the Section "Materials and Methods." Derived from psychoanalytic theory and the results from our previous paper (Schmeing et al., 2013), we put forward the following hypotheses. Subjects in the "apparent conflict" group should exhibit stronger reactions on multiple levels (behavioral, physiological, brain activity) to the conflict-related sentences than those in the "absent conflict" group. One question regarding the role of psychodynamic conflicts for an individual will additionally be tested in this study: is "having" a conflict better described as a trait or a state? That is, will subjects in the "apparent conflict" group exhibit the hypothesized stronger activity in reaction to *all* conflict-related sentences, regardless of the specific association to that sentence, because they generally tend to react strongly to that sort of content (trait)? More specific, subjects in the "apparent conflict" group could have the strong reactions only to the sentences that have actually produced the salient associations (state). To test this, analyses were carried out in a between-subject design (comparing "apparent conflict" and "absent conflict" subjects) and a within-subject design (comparing "conflict" and "no conflict" sentences only within the "apparent conflict" group). In detail, we assumed that the "apparent conflict" group should evaluate the sentences with a more negative valence (behavioral). On the physiological level, skin conductance reflecting autonomic arousal should be relatively higher in "apparent conflict" subjects when confronted with conflict-related sentences. Finally, brain activity in the ACC/pre-SMA [amongst other functions relevant for emotion processing (Etkin et al., 2011) and conflict monitoring (Botvinick, 2007)] should be enhanced in "apparent conflict" subjects. Since the ACC/pre-SMA was relatively more active when associating to conflict-related sentences in the whole group of subjects (Schmeing et al., 2013), differential activity of this region for only the "apparent conflict" group would strengthen the specificity of our findings. To this end, this study represents, in essence, an analysis of the behavioral, physiological, and brain data obtained in Schmeing et al. (2013), guided by the separation of all subjects into two groups based on the psychoanalytic content of their free associations. Although the current study was based on the same dataset, it focuses on the analysis of the *content* of the participants' free associations following conflict sentences, which was not investigated in our previous paper.

## MATERIALS AND METHODS

### ETHICS STATEMENT

The study was approved by the local medical ethics committee ("Ethikkommission an der Medizinischen Fakultaet der Rheinischen Friedrich-Wilhelms-Universitaet Bonn"), was according to the latest version of the Declaration of Helsinki, and all subjects provided written informed consent.

In **Box 1**, we provide an example of a free association from one participant, which was slightly modified to ensure that s/he cannot be identified. This participant signed an agreement that this text can be published.

### PARTICIPANTS

Participants were recruited through notifications on the homepage of the University of Bonn Students' Service. They were paid 10€/h (total time for the experiment 3.5–4 h). They were right-handed, native German speakers with normal or corrected-to-normal vision, and without current or past neurological or psychiatric disorders.

In the experiment, a total of 23 subjects were scanned, 5 of which were excluded from analysis because of high motion artifacts (more than one voxel diameter; 3 subjects), or early

**BOX 1 | An example of the clinical evaluation of trials.**

The following assessment of associations was performed based on the manual of operationalized psychodynamic diagnosis (OPD-Task-Force, 2008). The subject in the example shown here was classified as belonging to the "apparent conflict" group, consisting of individuals with at least one association reflecting a possible psychodynamic conflict. The following answer to one conflict sentence ("I only feel good when someone is actually taking care of me") has been chosen to provide the reader with an understanding of the rating process used.

OPD-conflict: desire for care vs. autarchy, *passive mode*

Following the OPD manual (OPD-Task-Force, 2008, p. 227–230) subjects who suffer from desire for care vs. autarchy conflict in passive mode can be described as being "dependent and demanding." They have the strong desire to be taken care of by others. As can be seen in the following example, such subjects tend to show high emotional attachment to others in their lives, try to avoid being alone or feeling lonely. In relationships, they can experience difficulties when separated from their partners. If the partner sets boundaries on the limits of care he/she is willing to provide, this can lead to feelings of depression, insufficiency, and fear of being alone.

Free associations of subject to the stimulus sentence: "I only feel good when someone is taking care of me:"

"Loneliness . . . to be left alone . . . social attachment. This sentence applies to me fully. *I believe I am a person who finds it difficult to be alone* (author comment: subject starts speaking more quietly) . . . I am a person who prefers being surrounded by people that aren't my first choice, rather than being alone. This was one of the issues that came up in my relationships. Both with my current girlfriend as well as with my previous girlfriend – we often had the issue that in the evenings she . . . well . . . let's say . . . leaves me by myself in front of the TV and goes to bed . . . or when she withdraws into normal domestic life and I am looking for much more contact . . . *well I am not the type of person with whom one can be in the same room for 2–3 hours and not talk, like someone who just sits in a corner* . . . (author comment: subjects is getting upset, speaking more loudly)"

interruption of the experiment (2 subjects). Of the 18 participants included in both fMRI and behavioral/SCR analysis (10 female), mean age was 25.9 ± 3.2 years (mean ± standard deviation).

## EXPERIMENTAL PARADIGM

All participants of the study were invited a few days before the experiment in order to practice the technique of free association and to screen them for psychiatric symptoms. For this screening, two questionnaires were used: SCL-90 (symptom check list) and BDI (Beck's Depression Inventory). Those who scored high on either of the questionnaires (cut-offs: BDI >11, SCL-90 Global Severity Index >0.57) were excluded from the experiment.

The experiment consisted of three parts: association phase (including a rating), break/distraction, and memory recall.

### *Association phase*

Subjects were placed in the MRI scanner, with video goggles to present stimuli (Nordic Neuro Lab, Bergen, Norway), a microphone to record verbal response (Fibersound® Microphone Model FOM1-MR and Fibersound® Control Model FOM1-DRx Battery/wall powered; Micro Optics Technologies Fibersound™ Audio, Middleton, WI, USA), and two electrodes connected to the right palm for SCR measurements. A hand-held four-button device was used for rating. A stimulus (one of 24 sentences, presented in random order) was shown for 5 s, followed by a 60 s time period (indicated by a question mark) for free association. During this total period of 65 s, the verbal responses of the subjects were digitally recorded. The participants were asked to say the first three words that came to their mind after stimulus presentation, and use the remaining time for (overt) free association. Afterwards, subjects rated their agreement with the sentence (on a scale ranging from 1: very strong disagreement to 9: very strong agreement), and their own emotional state after association in terms of valence (−4: very negative to +4: very positive feeling) and arousal (1: very calm to 9: very aroused). Rating was followed by a 30-s break. After an inter-stimulus-interval (fixation cross) of 1.5–3 s, the next stimulus was presented.

Of the 24 stimulus sentences, 6 were "neutral" and 6 were "generally negative," while the remaining 12 were "conflict related," meaning that they were designed to resemble typical expressions of psychodynamic conflicts. Those conflicts were selected on the basis of psychoanalytic theory and specified using the system of operationalized psychodynamic diagnosis (OPD; Cierpka et al., 2007; OPD-Task-Force, 2008). OPD is an instrument for the assessment of psychodynamic constructs (e.g., relation, conflict, structure). Two types of conflict were used for the generation of conflict-related sentences: autonomy/dependency (e.g., "I cannot say 'No' if someone else is asking me for help"), and self-esteem–conflict (e.g., "I often estimate myself as little competent"). Those two conflicts have been selected since they are most common among subjects suffering from interpersonal problems (Cierpka et al., 2007) and are operationalized in a very stringent and comprehensive way in the OPD manual. For each conflict, the manual provides anchor examples of typical manifestations regarding partnership, family, profession, behavior in groups, and others. The anchor examples served as a basis for the formulation of our stimulus sentences. Additionally, a state-licensed psychoanalyst not otherwise involved in the study confirmed the relevance of our stimuli. The neutral sentences described situations of mildly positive to neutral emotional content (e.g., "I try to follow the news on a regular basis"). The "generally negative" sentences included situations with negative value that could not typically be associated with a psychodynamic conflict (e.g., "Sometimes I am frightened when I walk alone in the dark"). A list of all sentences is provided as **Table 1**.

### *Break/distraction*

During the 1-h break/distraction phase outside the MRI scanner, subjects filled out the DSQ-40 questionnaire, designed to assess the prominence of maladaptive, adaptive, and neurotic defense mechanisms. There was no difference in DSQ-40 scores between the "apparent conflict" and "absent conflict" groups. This phase was mainly designed to distract subjects before the upcoming unexpected memory recall task.

**Table 1 | List of sentences.**

| |
|---|
| **Neutral sentences** |
| Occasionally I like to watch movies on the television |
| I try to follow the news on a regular basis |
| Sometimes my mood is influenced by the weather |
| There are topics I am more interested in than politics or economy |
| Mostly I do respect the traffic regulations |
| I find it important to find the time for my hobbies once in a while |
| **Negative sentences** |
| I am getting annoyed when I am stuck in a traffic jam and I have an important appointment |
| Sometimes I am frightened when I walk alone in the dark |
| When an overtaking car on the other side of the street approaches me, my heart sinks into my boots |
| Sometimes I become sad, when I think about dead soldiers in the war |
| Seeing a helpless animal suffer often makes me sad |
| When somebody is pushing in the line, it can really upset me |
| **Conflict sentences: desire for care vs. autarchy (passive)** |
| All my life I got a raw deal |
| I wish that finally someone is taking care of me |
| I have the feeling that I always get too little |
| I actually only feel good when someone is taking care of me |
| **Conflict sentences: desire for care vs. autarchy (active)** |
| I give so much, without getting really rewarded |
| I cannot say "No" if someone else is asking me for help |
| I do not need anything or anybody to be happy |
| I hate it to be a burden for other people |
| **Conflict sentences: self-value** |
| Usually I have a very low self esteem |
| I am often embarrassed about myself |
| Sometimes I am disgusted by myself |
| I often estimate myself as little competent |

### *Memory recall*

After the break, subjects had to perform an unexpected memory recall task. Again, they were placed in the MRI scanner with video goggles, microphone, and SCR-electrodes. All 24 sentences were presented again, after each of which subjects had 30 s to remember and name the 3 words that had come to their mind to that sentence in the beginning of the association phase in the first part of the experiment (not the content of the following free association phase). Again, answers were recorded via microphone. Only the first three answers were evaluated, and participants were encouraged to guess if they were unsure. The memory task was included because one of our original hypotheses, investigated in Schmeing et al. (2013), had been that associations with a long reaction time, and accompanied by a high SCR, were less likely to be remembered afterwards (see also Levinger and Clark, 1961; Rossmann, 1984; Kohler and Wilke, 1999). This subsequent forgetting may be a marker of repression during the free association period. In the current manuscript, activity related to cues was assessed regardless of the success of subsequent memory recall, because there was no difference in memory either between the "apparent conflict" and "absent conflict" groups or between "apparent conflict" and "absent conflict" trials within the first group.

Subjects were rewarded with 0.10€ for each correct answer afterwards, and for each incorrect or missing answer 0.05€ were subtracted from their total gain. Since audio recordings of association and recall had to be compared individually (by listening to them) in order to check if memory recall was correct, subjects received no immediate feedback about their performance.

Trials were considered valid and included into analysis if the participants had given three associations at the beginning of the association phase, and audio quality was good enough in both association phase and recall phase to allow for comparison. Successful memory recall was not required for trials to be considered valid and to be included into analysis.

## MRI DATA ACQUISITION AND ANALYSIS

Thirty-four axial slices were collected at 1.5 T (Avanto, Siemens, Erlangen, Germany). We collected T2*-weighted, gradient echo EPI scans (slice thickness: 3.0 mm; voxel size: 3 mm × 3 mm × 3 mm; matrix size: 64 × 64; field of view: 210 mm × 210 mm; repetition time: 2700 ms; echo time: 40 ms). Thereafter, we acquired a 3D-sagittal T1-weighted MPRAGE sequence for each subject for anatomical localization (number of slices: 160; slice thickness: 1 mm; inter-slice gap: 0.5 mm; voxel size: 1 mm × 1 mm × 1 mm; matrix size 256 × 256; field of view: 256 mm; echo time: 3.09 ms; repetition time: 1660 ms).

Activity was analyzed during the free association phase of the experiment, but not during the recall phase.

MRIs were pre-processed in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) using standard pre-processing steps including realignment, unwarping, normalization, and smoothing with a 6-mm Gaussian kernel. Pre-processed data were fitted by the convolution of multiple regressors with a canonical hemodynamic response function to obtain parameter estimates for each condition covariate.

Two different GLMs were used to compare reactions to conflict sentences between the "apparent conflict" and "absent conflict" group (conflict as a trait) and to compare reactions to conflict sentences that actually triggered a conflict and those that did not trigger a conflict within the "apparent conflict" group (conflict as a state).

Separate regressors were used to model transient activity directly after cue presentation (delta pulses, i.e., stick functions with a duration of $t = 0$, triggered to the onset of cue presentation) and more sustained activity related to free association (box-car regressors ranging from 5 s after stimulus onset until the end of a trial) for the neutral, negative, and conflict conditions. To model early activation, we used stick functions instead of box-car regressors in order to maximize comparability with our previous analyses reported in Schmeing et al. (2013), where stick functions were used as well. The rationale for this analysis is that we expected repression effects to occur rapidly after stimulus presentation, because cues trigger internal conflicts rapidly

and before a participant has finished generating a word for free association. This is supported by our findings from Schmeing et al. (2013), showing that reaction times differ as a function of sentence category. The content of the subsequent free association (which was analyzed in the current study) may then be a marker of the actual conflict generated by each sentence. Since the box-car regressors for sustained activity did not reveal any differences between the conditions, all contrasts and results reported in the results section refer to the early, delta-pulse regressors.

For the comparison between the "apparent conflict" and the "absent conflict" group, we used the following set of regressors:

(1) Regressor triggered to the onset of conflict sentence presentation regardless of apparent conflicts; duration = 0
(2) Regressor triggered to the onset of negative sentence presentation; duration = 0
(3) Regressor triggered to the onset of neutral sentence presentation; duration = 0
(4) Regressor triggered to 5 s after the onset of conflict sentence presentation for free associations, regardless of apparent conflicts; duration = 60 s.
(5) Regressor triggered to 5 s after the onset of negative sentence presentation; duration = 60 s
(6) Regressor triggered to 5 s after the onset of neutral sentence presentation; duration = 60 s
(7) Regressor triggered to the onset of the rating periods after each free association period (i.e., triggered to 65 s after the onset of each sentence presentation); since rating was self-paced, the duration of this regressor was variable
(8) Regressor triggered to the onset of the inter-stimulus break; duration = 30 s.

Another GLM was calculated for the analysis within the "apparent conflict" group. Here, regressors 1 and 4 were split into "apparent conflict" and "absent conflict," according to clinical evaluation. These are henceforth referred to as regressors 1A/1B and 4A/4B, respectively. All other regressors remained the same.

In our contrast analyses, we conducted two complementary approaches:

(A) Within the subgroup of participants who showed an apparent conflict in reaction to at least one conflict sentence, we contrasted beta values from regressor 1A vs. regressor 1B, and from regressor 4A vs. regressor 4B intra-individually. Then, a one-sample *t*-test was used to determine whether contrast means differed significantly from 0.
(B) For our between-groups analysis, we first calculated intra-individual contrasts between sentence conditions (regressor 1 vs. regressor 2; regressor 1 vs. regressor 3; regressor 2 vs. regressor 3; 2*regressor 1 vs. regressor 2 + regressor 3). Corresponding analyses were conducted for regressors 4–6. These contrasts were then compared between the "apparent conflict" and the "absent conflict" group, using a two-sample *t*-test.

In **Figure 1**, fMRI results are displayed using neurological convention (left hemisphere on the left side of the figure). To identify significant activations, we used an uncorrected voxel threshold of $P < 0.001$ and an additional cluster threshold of $p < 0.05$, corrected for multiple comparisons using the false discovery rate (FDR) procedure of SPM5. For the ROI analyses, two sources to identify the ACC/pre-SMA were used. First, the ACC/pre-SMA area found to be activated by conflict sentences as compared to negative sentences for all subjects [MNI coordinates: −6/4/48; reported in Schmeing et al. (2013)]. It was chosen because one of our goals was to validate the findings of Schmeing et al. (2013), and to show that the ACC activation observed was indeed due to the personal relevance of conflict sentences to the subjects. Therefore, we had the hypothesis that this area should be more strongly activated in the "apparent conflict" group, for whom at least some of the conflict sentences were of personal relevance, according to our clinical rating. Second, an anatomically defined ROI of ACC/pre-SMA was applied according to the automatic anatomic labeling toolbox for SPM [AAL; Tzourio-Mazoyer et al. (2002)].

### SCR ACQUISITION AND ANALYSIS

We collected the SCR data with a sampling rate of 1000 Hz with BrainVision Recorder Software. Data were corrected for MRI-artifacts using BrainVision Analyser 2.0. We down-sampled data to 200 Hz and low-pass filtered them at 5 Hz. The corrected data were analyzed using the software LEDALAB (Benedek and Kaernbach, 2010) to extract phasic electrodermal activity in an integral of 4.5–13.1 s after stimulus presentation. This interval corresponds to the mean peak time of SCR-curves ± 0.5SD (8.8 ± 4.3 s).

### CLINICAL EVALUATION OF TRIALS

The recorded free-association periods of all 12 conflict-related stimulus sentences were assessed post-hoc by two expert psychotherapists trained in psychoanalysis, unaware of subjects' ratings of agreement, valence, and arousal, and not involved in fMRI analysis (Katrin Best, Henrik Kessler). Assessment of associations was performed according to the manual of OPD (OPD-Task-Force, 2008) and building on psychoanalytic theory. The OPD manual provides detailed anchor examples of typical manifestations for each psychodynamic conflict, by listing emotions, thoughts, beliefs, behavior, transference, countertransference, relationship themes, and others that are most commonly associated with that conflict. Subjects' associations were compared with the anchor examples for the respective conflict covered in the stimulus sentence. If, for example, the stimulus sentence is covering the "autonomy-dependency" conflict, then associations dealing with feelings of envy towards others that presumably received more than the subject would point towards that very conflict playing a role. Of course, in the reality of assessing associations things were more complex and considered various aspects of the material provided by the subjects (e.g., prosody, wording, breaks, hesitation). The aim was to detect associations that point to probable psychodynamic conflicts regarding the theme of the stimulus sentence. Obviously, those conflicts could be conscious or unconscious, hence leaving the opportunity for direct confirmation of the agreement, valence, or arousal in reaction to a given stimulus sentence via subjects' ratings. The analysis of associations led to a separation of tested subjects into two groups: "apparent conflict" comprised individuals with at least one association reflecting a possible psychodynamic conflict; "absent

conflict" consisted of individuals who did not show any sign of conflict in their associations. Trials with conflict-related sentences were only included into analysis if a decision could be reached whether the trial was to be classified as "apparent conflict" or "absent conflict." Each association was evaluated completely by one expert (Katrin Best), and each rating was discussed with the second expert (Henrik Kessler). Whenever Katrin Best considered a rating insecure, it was independently evaluated by Henrik Kessler. Thus, all possible conflicts were thoroughly discussed between both experts until a consensus was reached. Because of our method of rating it is not possible to provide inter-rater reliability. An example of the evaluation process is provided in **Box 1**.

### STATISTICAL ANALYSIS

We conducted one-tailed tests if we had directed *a priori* expectations and two-tailed tests otherwise. In detail, we had the following directed hypotheses:

1. In a between-group analysis, group 1 subjects (showing at least one "apparent conflict") should in general react to conflict-related sentences with higher agreement, more negative valence, higher SCRs (autonomic arousal), and increased BOLD response in ACC/pre-SMA as compared to group 2 subjects (without any "apparent conflict" sentences).
2. Within group 1, higher agreement, more negative valence, higher SCRs, and increased BOLD response in ACC/pre-SMA to sentences rated "apparent conflict" compared to sentences rated "absent conflict" should be evident.

## RESULTS

### BEHAVIORAL AND SCR

Based on our clinical evaluation, 23 out of 209 valid trials were rated as "apparent conflict," equivalent to 11% of all trials. A proportion of 89% of all trials (186) were rated as "absent conflict." 8 of our 18 subjects showed free associations classified as "apparent conflict" in at least one trial. Their number of "apparent conflict"-trials ranged from 1 to 7 (8.3–58.3% of their trials; mean: 2.88 trials; SD: 2.36 trials). In this subpopulation of subjects, 23 out of 89 trials (or 26%) were classified as "apparent conflict," 66 were rated as "absent conflict" (74%).

At first, we looked for differences in behavioral measures between group 1 (those subjects who had an "apparent conflict" in at least one association period according to the clinical evaluation) and group 2 (those who showed no "apparent conflict" in their associations), comparing all trials with conflict-related sentences between those two groups. **Table 2** provides the results of this comparison. Subjects in group 1 reported a more negative mood after their association, indicated by more negative ratings of valence ($p = 0.007$, Mann–Whitney $U$-test, one-tailed), and showed a higher degree of agreement with the sentences compared with group 2 ($p = 0.028$, Mann–Whitney $U$-test, one-tailed). Also, they had significantly higher SCRs ($p < 10^{-4}$, $t_{209} = 4.15$, two-sample $t$-test, one-tailed).

Next, we investigated whether trials within group 1 subjects, classified by our clinical evaluation as "apparent conflict" or "absent conflict," could be discriminated by behavioral measures. **Table 3** provides the results from this within-group analysis.

**Table 2 | Comparison of valence and agreement ratings and skin conductance reactivity between group 1 with "apparent conflict" and group 2 with "absent conflict."**

| | Between-group analysis | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 "apparent conflict" | | Group 2 "absent conflict" | | *p* | *t* |
| | Mean | SD | Mean | SD | | |
| Valence rating | −0.04 | 1.78 | 0.51 | 1.52 | 0.007 | |
| Agreement rating | 3.7 | 2.39 | 3.31 | 2.54 | 0.028 | |
| SCR (μS*s) | 14.8 | 14.3 | 8.3 | 8.4 | $<10^{-4}$ | $t_{209} = 4.15$ |

*Valence and agreement compared using a Mann–Whitney U-test, SCRs compared using a two-sample t-test, both one-tailed.*

**Table 3 | Comparison of valence and agreement ratings and skin conductance reactivity only within group 1 with "apparent conflict" between trials with and without "apparent conflicts."**

| | Within-group analysis "apparent conflict" group | | | | | |
|---|---|---|---|---|---|---|
| | Apparent conflict trials | | Absent conflict trials | | *p* | *t* |
| | Mean | SD | Mean | SD | | |
| Valence rating | −1.39 | 1.59 | 0.38 | 1.60 | $<10^{-4}$ | |
| Agreement rating | 4.83 | 2.15 | 3.36 | 2.38 | 0.0033 | |
| SCR (μS*s) | 14.3 | 13.0 | 14.8 | 15.0 | 0.56 | $t_{87} = 0.16$ |

*Valence and agreement compared using a Mann–Whitney U-test, SCRs compared using a two-sample t-test, both one-tailed.*

Consistent with our findings from the between-groups analysis, valence ratings for "apparent conflict"-trials were more negative compared to "absent conflict"-trials ($p < 10^{-4}$, Mann–Whitney $U$-test, one-tailed) and there was a higher agreement with "apparent conflict" sentences ($p = 0.0033$, Mann–Whitney $U$-test, one-tailed). Contrary to our hypothesis though, a difference in SCR was not observed.

### FUNCTIONAL MRI RESULTS

We first performed a region of interest analysis of the ACC/pre-SMA area found to be activated by conflict sentences as compared to negative sentences [MNI coordinates: −6/4/48; reported in Schmeing et al., 2013]. **Figure 1** shows the location of this area and bar graphs depicting the comparisons. We found that in group 1 (with "apparent conflict"), this cluster was more strongly activated for conflict-related sentences compared to neutral sentences than in group 2 ($t_{16} = 2.56$; $p = 0.0106$; two-sample $t$-test, one-tailed) and for conflict-related sentences compared to both neutral and negative sentences (contrast: 2*conflict vs. [neutral + negative]; $t_{16} = 2.66$; $p = 0.0085$; two-sample $t$-test, one-tailed). An anatomical region of interest composed of bilateral ACC and SMA showed a difference between the groups for conflict-related sentences vs. both negative and neutral sentences ($t_{16} = 2.74$, $p = 0.0073$; two-sample $t$-test, one-tailed). Within-group comparisons between sentences comprising an "apparent conflict" and those with "absent conflict" yielded no significant results on the fMRI level. Also, there were no significant differences on the whole brain level either between the two groups or within group 1, with correction for multiple comparisons using the false discovery rate (FDR) procedure of SPM5.

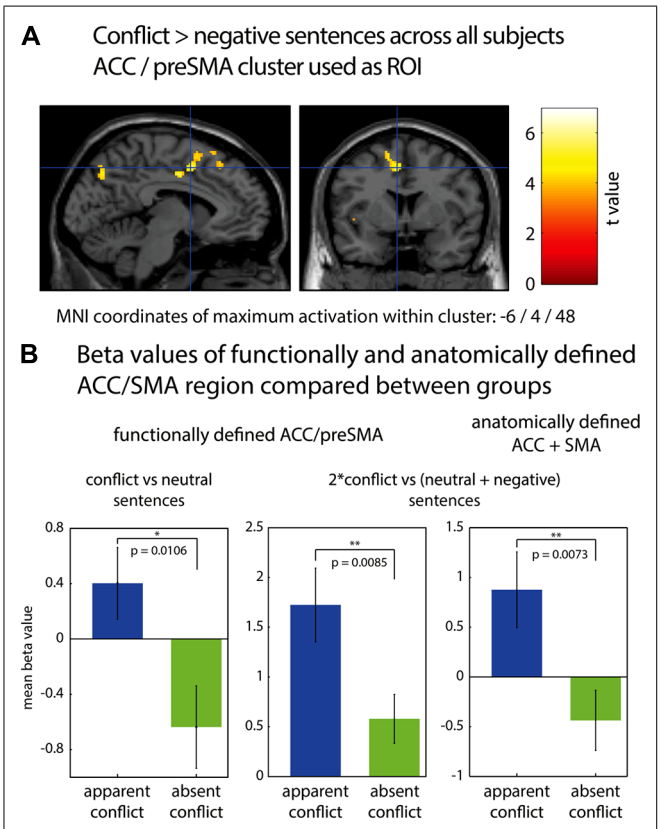


**FIGURE 1 | (A)** fMRI cluster including parts of ACC and preSMA, found to be activated during association to conflict-related sentences compared to negative sentences (Schmeing et al., 2013). **(B)** Comparison of mean beta values in functionally and anatomically defined regions of interest between group 1 ("apparent conflict") and group 2 ("absent conflict"), using a one-tailed two-sample $t$-test. Bar plots indicate mean values with SEM. $*p < 0.05$; $**p < 0.01$.

## DISCUSSION

We presented a pilot study tapping into the concept of psychodynamic conflicts, in which we investigated the behavioral, physiological, and brain activation profiles during free association to putatively conflict-related sentences. All subjects were confronted with stimulus sentences describing typical psychodynamic conflict themes and had to associate spontaneously to them. Subjects' associations were then analyzed based on psychoanalytic theory and the system of OPD (OPD-Task-Force, 2008). This led to their separation into two groups: Group 1 consisted of individuals where the conflict-related sentences actually touched a "sore spot," meaning that the conflict is of relevance for them. Group 2 included subjects where associations to the sentences were free of any sign of psychodynamic conflict. With this individualized and psychoanalytically informed approach in data analysis, our results show differences between groups that can be interpreted as a possible correlate of psychodynamic conflict processing. In comparison to group 2, group 1 reported more agreement with the material of the conflict-related sentences, more negative valence and exhibited higher SCR. Additionally, subjects in group 1 specifically had enhanced activation in ACC/pre-SMA during processing of conflict sentences.

According to our hypothesis, specific activity in the "apparent conflict" group should reflect their reactions to the confrontation with psychodynamic conflicts and probably regulatory processes involved spontaneously. In clinical practice, the degree of consciousness of such reactions depends on the conflict itself and the level of coping with it (Brenner, 1982; Mentzos, 1984; Person et al., 2005). Since our subjects reported higher agreement with the contents covered in the conflict-related sentences, it is likely that their reactions and probable regulation take place consciously and that they are aware of the problems mentioned. It is therefore unlikely that our sentences touched unconscious (i.e., deeply buried, repressed) conflicts but rather the level of conflict where an awareness and ways to cope with it exist. Since we deliberately included only subjects without current or past psychiatric disorders, this result is not surprising, though. Yet, as "apparent conflict" subjects reported relatively more negative valence after the conflict-related sentences and their associations, the material presented had an emotional meaning and caused a subjective impact. The enhanced skin conductance reactions strengthen this effect and indicate that the confrontation with psychodynamic conflicts could have led to autonomic arousal. The latter point has already been hypothesized and in fact empirically shown by other researchers including Jung (Jung, 1918; Levinger and Clark, 1961; Kohler and Wilke, 1999). As for differences in BOLD responses, specific activity in the ACC for the "apparent conflict" group can also be interpreted in the vein of relatively

conscious processing of conflicts. The ACC region with differential activity is, amongst other functions, involved in emotional processing in general (Murphy et al., 2003; Etkin et al., 2011) and is supposed to play a key role when attending to subjective emotional responses (Lane et al., 1997). Following the old dichotomy of ACC subdivisions (Bush et al., 2000), the area of our ACC activation lies in the cognitive subdivision. Recent conceptualisations, though, argue for the involvement of the whole ACC in emotional processing with the dorsal-caudal regions (where our area can be localized) reflecting appraisal of negative emotions (Etkin et al., 2011). This ACC activity could thus be a neural correlate of subjects' emotional arousal in accordance with reports in self assessments (valence) and measured by skin conductance. In vein of this, our activation site lies in the dorsal anterior cingulate cortex (dACC), which also forms part of the so-called salience network (Seeley et al., 2007). Activity in this salience network might reflect subjects' arousal when confronted with the conflict (salient) sentences. It might also be that enhanced dACC activation is part of a defensive process (repression), where subjects "block" true self-reflection. This speculation would be in line with the ideas expressed in Axmacher et al. (2010), where it is argued that repression hinders the integration of memories with self-referential processes. Additionally, the dACC has recently been discussed to be part of a brain system processing social disconnection and painful affects (neural alarm system concerning threat-related responding) in human relations (Eisenberger and Cole, 2012). Hence, the conflict-related sentences could have served as stimuli evoking memories or fears of social disconnection in some subjects. This line of interpretation would be well consistent with the psychodynamic interpretation that some conflict sentences induce painful affects that lead subsequently to repression of associated contents. Indeed, in a previous study in patients undergoing psychodynamic group therapy, we found that negative (painful or aggressive) feelings during confrontation with unresolved conflicts were associated with activation of the ACC as well (Axmacher and Heinemann, 2012). Consistent with our results presented here, these unresolved conflicts were consciously aware to the patients. However, they were often not able to fully accept and tolerate their associated feelings – in other words, these feelings were isolated (a specific defence during which events themselves are not repressed, but associated feelings are; Freud, 1915, p. 153). Although the account of the ACC being involved in conflict monitoring regards information processing in a stricter sense (Botvinick, 2007), it is interesting that the processing of psychodynamic conflicts seems to recruit a similar area.

Our additional question was whether our separation between "apparent conflict" and "absent conflict" reflects a trait (subjects tend to view all sentences as problematic) or rather a state (just the sentences with conflict-related associations cause emotional reactions). Results tend to confirm the conceptualization as a trait. Subjects did rate the sentences with eventual conflict-related associations with more agreement and negative valence. This is in line with the above mentioned assumption that processing of conflicts is rather conscious. The lack of differences in skin conductance (arousal) and brain activity between the two types of sentences speaks against the idea that only the sentences leading to problematic associations have an emotional impact (state). We assume that "apparent conflict" subjects generally tend to show emotional reactions to that type of sentences.

In the vein of this special issue on psychoanalytic neuroscience, the results of our study make a point for the fruitfulness of applying psychoanalytic theory to neuroscientific research. Stimuli were derived from features of typical psychodynamic conflicts and transferred into an fMRI design. It is intriguing that free association, the classical technique most commonly used in psychoanalysis, could be a powerful tool to investigate aspects of conflict processing in neuroimaging, and that the quality of those associations could be used as a genuinely psychodynamic marker to separate subjects into two groups. Other forms of analyses of the associations would have been possible, e.g., qualitative content analysis (Mayring, 1983) or grounded theory (Glaser and Strauss, 1967). Yet, our aim was to stay within a psychoanalytic framework regarding stimulus production and assessment of the associations in order to view the material in a holistic rather than fragmented way. We do think that the general approach of our study could be implemented in other forms of research in neuropsychoanalysis in a fruitful way. Possibilities for future research include the use of individualized stimuli (generated, e.g., through diagnostic OPD-interviews) or recruitment of clinical patients with disorders traditionally believed to result from repressed conflicts (e.g., conversion disorders, or psychogenic, non-epileptic seizures).

### LIMITATIONS

One limitation of the study concerns the sample size. The comparisons between group 1 ("apparent conflict") and group 2 ("no apparent conflict") included actually 8 vs. 10 subjects. It is of notice that we obtained significant results with such a small sample size on the group level, but nevertheless, generalizability of results and hence ecological validity remain uncertain. A second limitation lies in the method of the group separation. Raters are experienced psychotherapists trained in psychoanalysis and OPD. They were blind to subjects' self-reports concerning the sentences and to the process of fMRI analysis. Still, as in any clinical setting, the final decision whether the association to a given sentence actually covers aspects of a psychodynamic conflict of this person remains uncertain.

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# Operationalized psychodynamic diagnosis as an instrument to transfer psychodynamic constructs into neuroscience

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This theoretical article makes a contribution to the field of "psychoanalytically informed neuroscience". First, central characteristics of psychoanalysis and neuroscience are briefly described leading into three epistemic dichotomies. Neuroscience versus psychoanalysis display almost opposing methodological approaches (reduction vs. expansion), test quality emphases (reliability vs. validity) and meaning of results (correlation vs. explanation). The critical point is to reach an intermediate level: in neuroscience an adequate position integrating both aspects—objective and subjective—of dual-aspect monism, and in psychoanalysis the appropriate level for the scientific investigation of its central concepts. As a suggestion to reach that level in both fields the system of Operationalized Psychodynamic Diagnosis (OPD; OPD Task Force, 2008) is presented. Combining aspects of both fields areas, expansion and reduction as well as reliability and validity, OPD could be a fruitful tool to transfer psychodynamic constructs into neuroscience. The article closes with a short description of recent applications of OPD in neuroscience.

**Keywords: neuroscience, psychoanalysis, neuropsychoanalysis, operationalized psychodynamic diagnosis, individualization, fMRI**

## INTRODUCTION

Despite many efforts to bring psychoanalysis and neuroscience together, we propose that there exists a profound gap between the two approaches. Hence, the intention of this theoretical article is, first, to describe those core differences and provide possible explanations for them and, second, to present the system of Operationalized Psychodynamic Diagnosis (OPD; OPD Task Force, 2008) as an instrument to bridge both sides. Although there exists a long (and eventful) relationship between psychoanalysis and different forms of neurosciences, the term "neuropsychoanalysis" itself was only coined in 1999 with the title of the respective journal. In an attempt to bring psychoanalysis and neuroscience together, pioneers in the field, Mark Solms and Oliver Turnbull, describe two scientific areas that fall under their broad conception of neuropsychoanalysis (Solms and Turnbull, 2011). First, they refer to the direct psychoanalytic investigation of neurological phenomena. This was the starting point of their work in the field using mainly patients with focal brain damage (Kaplan-Solms and Solms, 2000). Second, they also include psychoanalytically informed neuroscience, where hypotheses derived broadly from psychoanalysis are tested with neuroscientific methods. It is only the second aspect of neuropsychoanalysis that will be the subject of this article. On the theoretical and empirical side, many endeavors bringing both fields together could be observed which were mainly propelled by methodological and conceptual progresses achieved in neuroscience. Those endeavors are covered in the review by Sauvagnat and colleagues (Sauvagnat et al., 2010). Looking at institutions and structures, the founding of the "International Neuropsychoanalysis Society" and its respective journal *Neuropsychoanalysis* was a major step towards "building bridges between psychoanalysis, neuroscience, psychology and psychiatry" (full header on the society's website). Importantly, the society members and editorial staff of the journal include prominent scientists from both fields. This special issue on neuropsychoanalysis in *Frontiers in Human Neuroscience* is another venture assisting the "genuine dialogue between biology and psychoanalysis" (Kandel, 1999).

So far, there seem to be co-operations and exchanges between the two fields. Nevertheless, we still notice a strong reductionism in neuroscience and, more importantly, biological psychiatry. Psychoanalytic concepts seem to be virtually absent in major publications reporting empirical contributions in biological psychiatry. It is important, at this point, to introduce the differentiation between methodological and ontological reductionism. Only the latter, the idea that mental disorders *are* merely wrongly wired neurons or imbalances in certain transmitters and that it is of no relevance to consider psychological aspects (ontological reductionism) is questioned here. The *methodological* reductionism is a necessary prerequisite of neuroscience, stressing the importance to reduce complex phenomena into components that can be studied with neuroscientific methods. This form of reductionism is further described in the next section and actually forms one aspect where both, neuroscience and psychoanalysis, could be connected. On the psychoanalytical side there are still articles questioning the value of neuroscience to psychoanalysis in principle (Blass and Carmeli, 2007). Harder to capture within the scope of a scientific article though, but an important part of our reality, is the fact that there are psychoanalysts questioning the

approaches, methods and results of existing neuropsychoanalytic empirical work in seminars and discussion forums. There seems to be a profound scepticism towards attempts to bridge the two areas.

Our critical point is that the gap is not merely a problem of different scientific languages. From our point of view, the differences between neuroscience and psychoanalysis go deeper and can be dichotomized into almost opposing methodological approaches (reduction vs. expansion), test quality emphases (reliability vs. validity) and meaning of results (correlation vs. explanation). This will be embellished in the next section. Two intersections follow that are concerned with the problem to reach an intermediate level in both, psychoanalysis and neuroscience. Afterwards, OPD as a system will be presented, and the last section explains how OPD could help to transfer psychodynamic constructs into neuroscience, propelling empirical research in the field that Solms and Turnbull (2011) named "psychoanalytically informed neuroscience".

## CHARACTERISTICS OF PSYCHOANALYSIS AND NEUROSCIENCE

When considering differences between psychoanalysis and neuroscience one has to be aware of the divergent aims of both approaches. Whereas psychoanalysis was developed as a genuinely therapeutical technique to help the individual patient regain mental health, neuroscience wants to uncover the neural foundations of mental processes on an experimentally controlled level intentionally abstracting from the individual. From those divergent aims, different characteristics can easily be derived.

In psychoanalysis, the starting point is a clinical problem, i.e., a patient seeking for help from the psychoanalyst because he or she suffers from some form of mental disorder. To better understand the patient, the psychoanalyst eventually gathers information "surrounding" the problem: biographical background, recent circumstances of living and at work, situations triggering the problem, interpersonal relations, wishes, hopes, fears, complaints, dreams, and many more. That information is obtained by listening to the patient with "evenly suspended attention" (Freud, 1914) and sometimes asking direct questions. In other words: the initial clinical problem ("I feel depressed") is *expanded* into various branches of the patient's life and environment, in width and depth, to obtain a more comprehensive picture. All of this time-consuming process has the goal to, plainly spoken, "find out what really bothers the patient". That is, what are the factors that cause and eventually maintain the patient's clinical problem? Those factors could be idiosyncratic ways of interpersonal relations, certain psychodynamic conflicts or structural deficits. All of those factors are mainly rooted in the patient's biographical experiences (Person et al., 2005), the emotional and behavioral reactions towards those experiences, and finally the mental representation of this idiosyncratic experience and behavior. In psychoanalysis the idea of psychic determinism (Brenner, 1974) is of central importance: the above mentioned factors are believed to play a genuinely causal role in the development of the individual problem. This leads to two epistemic consequences. First, gathering information and factors can only be fruitful, if it deals with themes that actually apply to the individual, that are "truly his issues". Hence, on the level of test quality (although a psychoanalyst would hardly use the term regarding his practice), *validity* is of key importance. Second, causal inferences from psychological factors to clinical problems allow for an *explanation* of the latter. Dysfunctional relationship patterns with the parents could, for instance, explain the patient's problems in recent relationships leading to social isolation and depressed mood. *Expansion, validity* and *explanation* are thus three epistemic hallmarks in the practice of psychoanalysis.

As for neuroscience, the need for experimental control and abstraction from the individual call for almost opposing characteristics. When designing an experiment dealing with a certain psychological process, the inherent complexity of that very process has to be strictly controlled in order to achieve any meaningful results at all. One typical way of control is the *reduction* of a complex process into simpler components, which themselves are subject to the empirical investigation. Only relatively simple (sub-) components can be varied systematically in order to find regularities and differences in their characteristics. Furthermore, systematic experiments should be replicable. Investigating group effects for a certain psychological process and abstracting from individuals, different labs should principally obtain the same results using the same experiment. Hence, *reliability* is the central issue from a test quality perspective. Finally, due to well-investigated methodological constraints (e.g. Logothetis, 2008), results obtained with the most common neuroscientific methods (e.g., neuroimaging) reflect merely psycho-physiological co-activation. That is, the activity of certain brain areas that timely co-occurs with an observed psychological process is typically interpreted as the neural *correlate* of this very process. Thanks to the caution of serious neuroscientists, causality would not be inferred from this activity. Consequently, though, the measured brain activity cannot explain the psychological process. *Reduction, reliability* and *correlation* are hence the neuroscience counterparts of the above mentioned aspects in psychoanalysis.

## INTERSECTION I: REACHING THE INTERMEDIATE LEVEL IN NEUROSCIENCE

We dichotomized psychoanalysis and neuroscience in the previous section, but in fact profound differences in perspective exist even within each area. This shall be outlined briefly. As for neuroscience (and adjacent disciplines), a core—and very old—problem remains the question how brain and mind relate, that is, how can we bring together two entities that are apparently so different. Many endeavors in philosophy, psychology and other disciplines have been made to tackle this issue, but in the growing field of neuropsychoanalysis a position prevails that can be described as dual-aspect monism or perspectivism (see Solms, 1997 and Solms and Turnbull, 2002 for a detailed description and an overview of the debate). The central idea is that mind and brain are the same (monism), but we perceive them from two different perspectives (dual-aspect). As neuroscientists we focus on the physiological and anatomical aspect of the mind/brain from an "objective" perspective, and as human beings we perceive it from the inside in a "subjective" way.

Regardless of how we see it, mind/brain remains one entity. Sigmund Freud also adopted this "intermediate" position and provided us with the technique of free association as a means to explore the inner, subjective, aspect of mind/brain. The two premises of dual-aspect monism—mind and brain are one that we can perceive from two perspectives—actually form the very foundation of the neuropsychoanalytic venture. The "monism" part is implicitly included when researchers like Eric Kandel state in an influential article bridging psychiatry and biology: "Insofar as our words produce changes in our patient's mind, it is likely that these psychotherapeutic interventions produce changes in the patient's brain" (Kandel, 1998, p. 466). In this article, Kandel understands interactions between brain, mind and behavior on a broad level: behavior and social factors exert actions on the brain by feeding back upon it to modify gene-expression and thus nervous functioning. It is hence the belief that psychosocial experiences actually have an impact on the physical brain, that relationship patterns leave their traces in neural networks that fuels the research in neuropsychoanalysis. The true art is, of course, to reach that intermediate level in neuroscience where both perspectives—the objective and subjective—can best be integrated. The application of OPD in neuroscientific research (see last section) is an attempt to reach that level.

## INTERSECTION II: REACHING THE INTERMEDIATE LEVEL IN PSYCHOANALYSIS

Psychoanalysis itself is facing the difficulty to reach an intermediate level appropriate for the scientific investigation of its central concepts. Hence, a brief introduction into the problem of operationalization in psychoanalysis is provided before describing the system of OPD itself.

Attempts to operationalize psychoanalytic concepts are inevitably encountered with challenging difficulties. The central task of the operationalization of a construct must be to establish a link between the levels of theory and observation. Research operationalizations are primarily geared towards the logic of experimental design, and in this way substantially influence the translation of the original theoretical term into an operational term. For this, it is necessary to explicate and specify the relevant constructs in order for them to be translated into research operations. This step is difficult in psychoanalysis with its complex constructs like the unconscious, processes of repression, affects, or transferences which are not directly observable but must be inferred from their "derivatives". Therefore endeavors of operationalization of psychoanalytic concepts must reach an intermediate level, which may allow a gain in clarity and unequivocalness, without at the same time removing the concept too far away from its dynamic content. To emphasize, the goal of such a procedure would be to gain as much freedom from contradiction as possible while preserving as much dynamic content as possible.

## OPERATIONALIZED PSYCHODYNAMIC DIAGNOSIS (OPD)

As for the "standard" assessment of mental disorders the "Diagnostic and Statistical Manual" (DSM-IV) of the American Psychiatric Association (APA, 1994) and the "International Classification of Mental and Behavioral Disorders" (ICD-10) of the World Health Organization (WHO, 1992) have attained wide usage. Psychodynamic psychotherapists (and others) regret, however, the lack of relevance of the phenomenological and symptom-centered diagnoses of ICD and DSM when seeking possible explanations of clinical problems. On the other side, there was a growing dissatisfaction with the divergence of psychoanalytic theory: different groups vary in terminology and develop their own (sub-) concepts, rendering communication between therapists difficult. Those two problems were the starting point for the creation of the OPD Task Force in 1990 in Germany. The goal was to broaden the ICD and DSM classifications to include fundamental psychodynamic dimensions, and at the same time to remain aspects of reliability and terminological precision apparent in ICD and DSM. In reference to the previous section, OPD is an attempt to reach the intermediate level.

The OPD system is based on four psychodynamically relevant diagnostic axes with appropriate categories to complement ICD classification (fifth axis): axis I (experience of illness and prerequisites for treatment), axis II (interpersonal relations), axis III (psychodynamic conflicts), axis IV (psychological structure) and axis V (syndromal diagnosis according to ICD-10).

In practice, for a 1–2 h patient examination, which is still an open psychodynamic interview in nature, OPD provides flexible interview guidelines to ensure the relevant information is obtained. Details can be found in the recent OPD manual (OPD Task Force, 2008). The three axes most relevant for the psychodynamic approach will be described briefly.

As for axis II (interpersonal relations), mental disorders are conceived as "relationship disorders". In almost all schools of psychotherapy, automated and maladaptive interpersonal behavior patterns are considered to be an essential factor influencing mental disorders. Along with symptomatic complaints, problems relating to interaction with others are often the most important factor to be addressed at the outset of psychotherapy. With time, through the "depositing" of relational experiences, mental representations develop alongside the life story, and these are confirmed or modified by our experiences in interpersonal relationships with others (Anchin and Kiesler, 1982). The basic structure of the OPD relationship axis depicts the circular or transactional character of human interaction (interchange of subjective experience and response to the environment). A framework was developed which encapsulates subjective experience concerning self and others on the initial level. On a second level it is possible to represent the experience of this other person (significant other, interviewer): how is the patient experienced by his objects or the interviewer and which impulses does he generate in them? Items of the OPD relationship axis help to define the variety of behaviors seen in relationships.

Axis III assesses psychodynamic conflicts searching for common motives in central life areas such as relationship to partner, family of origin, profession, ownership, behavior in groups and illness experience. OPD distinguishes the following seven conflicts: (1) Dependence versus autonomy; (2) Submission versus control; (3) Desire for care vs. autarchy; (4) Conflicts of self-value; (5) Guilt conflicts; (6) Oedipal conflicts; (7) Identity conflicts. Those conflicts are operationalized thoroughly in the manual, providing a terminologically clear description of the con-

flict characteristics, its typical core affect, transference, countertransference and implications for various aspects of the patient's life.

Finally, the fourth axis is concerned with the psychological structure of the patient. OPD differentiates four levels of structure (good integrated, moderately integrated, low integrated, disintegrated). Good integration means that an autonomous self possesses a mental internal space in which mental conflicts can be carried out. Moderate integration implies lower availability of regulating function and a weaker differentiation of mental substructures. With low integration the mental inner space and substructures are less developed, thus conflicts are barely mentally worked out, but are mainly worked out in the interpersonal sphere. Disintegration is characterized by fragmentation and psychotic restitution of the structure. Operationalization of structure is based on four structural dimensions with a self-related and an object-related subdomain each: (1) Perception; (2) Regulation; (3) Communication; (4) Bonding. Again, those structural levels are operationalized extensively with clear descriptions and patient examples to illustrate specific structural deficits.

Concluding this section, OPD combines the best of both approaches: the inclusion of an expanded view apparent in psychoanalysis and the systematic reduction helpful in all experimental sciences (e.g. neuroscience). Due to the consideration of psychoanalytical constructs that are well-grounded in clinical experience, validity of the OPD is sufficient, and because of the systematic operationalization of assessment, reliability is constantly high in empirical investigations (Cierpka et al., 2007).

## THE TRANSFER OF PSYCHODYNAMIC CONSTRUCTS INTO NEUROSCIENCE

As a starting point, we do believe that psychoanalysis and neuroscience could substantially benefit from each other in the field of "psychoanalytically informed neuroscience" (Solms and Turnbull, 2011). The key question regards an adequate methodological approach to bring the two together. Being the main message of this article, we want to propose OPD as an instrument to transfer psychodynamic constructs into neuroscience. Advanced neuroscience methods offer superior experimental control and fine-grained analyses of brain activation and connectivity. This rigorous method is the bottom line for any scientific investigation of complex mental phenomena. To avoid the shortcomings of reductionism, that necessarily come with experimental control, an expansive tapping into real-world complexity should be tried, however. One important way to achieve this is via individualization of experiments, as has been proposed before (Kessler et al., 2011b). Only if the experiment touches the mentally represented themes that are of individual relevance to each subject, results could have validity and meaning in a deeper sense. But how can we gather individualized information in a systematic way that is compatible with experimental control? This is where OPD offers the system and practical tools for the task at hand. First, real-life complexity of actual patients is *reduced* into simpler components in a methodologically rigorous and transparent way as reflected in the axes and the differentiation between items within a given axis. The good operationalization of the OPD manual fosters *reliability*, and the richness (*expansion*) of the material obtained in an individual interview provides the basis for *validity*. Second, the components assessed with OPD can be translated into experimental stimuli with relative ease (see below). Brain reactions to those stimuli could be interpreted on a better foundation due to the individual and valid nature of the stimuli. This clinically-grounded *explanation* of brain activity must not, however, be confused with causality in a strict sense. Since there are always alternative directions to consider brain activity (see Lewis, 2000 and Kessler et al., 2011b for details) the quest for causality has to remain an open issue.

In the remainder of this section we want to give recent examples of how OPD is used in neuroscience. With space constraints and the focus of this article on the theoretical aspects, this part is kept short and serves mainly for illustratory purposes. Details can be found in the respective publications. The first study in this vein investigated patients with chronic depression undergoing psychoanalysis (Kessler et al., 2011a). An OPD interview was conducted with each patient to extract his or her major dysfunctional repetitive relation leading to depression or maintaining it. This pattern was translated into four essential sentences presented in the fMRI scanner (block design, 30 s for all four sentences). An example set would be: "You wish to be accepted by others. Therefore you do a lot for them. That is often too close for them, so they retreat. Then you feel empty and lonely". Patients exhibited relatively strong activation in limbic and subcortical areas (e.g., amygdala, basal ganglia) reflecting possible emotion processing. The critical issue here is that brain responses to those stimuli can be interpreted on a clinical ground due to the individualized nature of the stimuli. In another study, OPD was used to derive sentences that capture the essence of typical psychodynamic conflicts (Schmeing et al., 2013). Those sentences served as stimuli in an fMRI experiment investigating free associations to potentially conflictual situations in healthy participants. Two types of conflict were used for the generation of "OPD" sentences: autonomy/dependency (e.g., "I cannot say "No" if someone else is asking me for help"), and self-esteem–conflict (e.g., "I often estimate myself as little competent"). Again, with the stimuli themselves being rooted in OPD, brain activity during free association to those sentences could have a psychodynamic "meaning". Finally, in a recent study from our lab fMRI data is collected during free association to emotionally relevant sentences and analyzed using an OPD-based separation of subjects into two groups: (1) individuals with the association reflecting a possible psychodynamic conflict; (2) individuals who did not show any sign of conflict in their associations (Kehyayan et al., 2013). To this end, subjects' associations were compared with the typical manifestations of the respective psychodynamic conflicts described thoroughly in the OPD manual (partnership, family, profession, etc.). The aim was to detect associations that point to probable psychodynamic conflicts regarding the theme of the stimulus sentence. OPD is thus used post-hoc to provide a psychodynamic interpretation of brain activity.

## CONCLUSION

In the face of profound differences between psychoanalysis and neuroscience, the critical point is to reach an intermediate level.

That is, an adequate position to integrate the subjective and objective aspect of dual-aspect monism and the appropriate level to systematically investigate concepts of psychoanalysis. In this vein, the best aspects of both approaches have to be included (e.g., systematic reduction and at the same time clinically relevant expansion or reliability maintaining validity). OPD is presented as such an approach to reach that level by transferring psychodynamic constructs into neuroscience.

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# On the physiology of jouissance: interpreting the mesolimbic dopaminergic reward functions from a psychoanalytic perspective

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*Jouissance* is a Lacanian concept, infamous for being impervious to understanding and which expresses the paradoxical satisfaction that a subject may derive from his symptom. On the basis of Freud's "experience of satisfaction" we have proposed a first working definition of *jouissance* as the (benefit gained from) the motor tension underlying the action which was [once] adequate in bringing relief to the drive and, on the basis of their striking reciprocal resonances, we have proposed that central dopaminergic systems could embody the physiological architecture of Freud's concept of the drive. We have then distinguished two constitutive axes to *jouissance*: one concerns the subject's body and the other the subject's history. Four distinctive aspects of these axes are discussed both from a metapsychological and from a neuroscience point of view. We conclude that *jouissance* could be described as an accumulation of body tension, fuelling for action, but continuously balancing between reward and anxiety, and both marking the physiology of the body with the history of its commemoration and arising from this inscription as a constant push to act and to repeat. Moreover, it seems that the mesolimbic accumbens dopaminergic pathway is a reasonable candidate for its underlying physiological architecture.

**Keywords: neuropsychoanalysis, jouissance, enjoyment, Lacan, addiction, reward, dopamine, psychoanalysis**

## INTRODUCTION

We previously proposed physiological frameworks to understand a number of psychoanalytic concepts like repression and primary process, as well as the Lacanian concept of the signifier (Bazan, 2006, 2007, 2009, 2011, 2012; Bazan and Snodgrass, 2012). The topic of the present paper will be another Lacanian concept, *jouissance*, which is quite untranslatable but has been translated before as *enjoyment* (Evans, 1996). The concept itself is also infamous for being impervious to understanding. Because the concept appears relatively late in the teaching of Lacan, and only by bits and pieces, we chose to start with a clinical description. Indeed, clinical experience leads us to unmistakably identify a human tendency to seek, beyond the mere pursuit of pleasure, for that which brings the subject into danger or for that which sabotages his life. In its purest clinical form *jouissance* is what explains why people are addicted to harmful, or even lethal, substances – e.g., why people cannot stop smoking even after being diagnosed with lung cancer. *Jouissance* thus expresses the paradoxical satisfaction that the subject derives from his symptom (Evans, 1996, p. 92). In *Mourning and melancholia*, for example, Freud (1917/1914–1916, p. 251) says literally: "The self-tormenting in melancholia, (which) is without doubt enjoyable:" the melancholic subject also gains satisfaction from self-devaluation. *Jouissance* is a crucial concept for clinics, as it explains why, against all rationality, subjects are often wedded to their problems, be it at the highest price, i.e., at the cost of their professional career, of their relationships or of their mere lives.

In the early seminars, Lacan (1975/1953–1954; 1978/1954–1955) uses the term with a reference to its original, juridical, meaning: the term arose in the XV century, to designate *the action of using a property for the purpose of obtaining the satisfaction it is supposed to provide*. It is akin in its meaning to the juridical concept of "usufruct," which is a *right of enjoyment, enabling a holder to derive profit or benefit from property that either is titled to another person or which is held in common ownership, as long as the property is not damaged or destroyed*. There is an essential distinction to take from these juridical definitions, which founds the notion of *jouissance*: it is the distinction between the satisfaction of *consuming* something, whereby it could be damaged, destroyed or lost in the consumption, and the satisfaction of *using* something with this satisfaction being explicitly not tied to its consumption. Several Lacanian authors explicitly use this definition of *jouissance* in its original juridical reference: e.g., Robin (2006, p. 29), in the context of addiction, defines enjoyment as the profit one can obtain from something which he does not possess. Jadin (2012/2009, p. 42) explains that abuse could be defined as "treating the body of the child as if one had usufruct of it."

Later on in Lacan's work, the sexual connotations of *jouissance* become more apparent. It is in *The Ethics of Psychoanalysis*, then, that (Lacan, 1986/1959–1960, p. 209) proposes that "jouissance appears not purely and simply as the satisfaction of a need, but as the satisfaction of a drive." Indeed, up to 1957, the term seems to mean no more than the enjoyable sensation

that accompanies the satisfaction of a biological need such as hunger (Lacan, 1994/1956–1957, p. 125), but in this seminar *jouissance* and pleasure are distinguished. It is therefore that, starting precisely from Freud's model of drive, we will propose a metapsychological understanding of the concept of *jouissance* which will allow for an operationalisation in physiological terms. We have organized our paper in two parts, a psychoanalytic (metapsychological) part followed by a (neuro-)physiological part. Moreover, we have distinguished two constitutive axes to *jouissance*: one has to do with the *body* and entails the aspects of (1) the drive, (2) the experience of satisfaction and (3) the dimension of excess (of body tension); the other has to do with the (subject's) *history* and basically entails the commemoration of a trait, complying to repeat. These four distinctive aspects are respectively discussed both from a metapsychological and from a neuroscience point of view.

## METAPSYCHOLOGY: FROM BODY TO HISTORY

### BODY

#### *Freud's model of the drive*

In Freud's (1915) model, a drive has a source (a biological need or lack), an aim (the satisfaction of that need), an object (adequate in satisfying the need) and an impetus (a pressure pushing to act). Hunger could, in this model, start with a biological signal, such as low blood sugar sensed in the lateral hypothalamus (LH). This lack is sensed by the central nervous system (symbolized by ψ in Freud's *Project*) where the lack accumulates as an excess of endogenous quantities: "The nucleus of ψ is connected with the paths by which endogenous quantities of excitation ascend. (…) The filling of the nuclear neurones in ψ will have as its result an effort to discharge, an *urgency* which is released along the motor pathway. Experience shows that here the first path to be taken is that leading to *internal change* (expression of emotions, screaming, vascular innervation). But no such discharge can produce an unburdening result, since the endogenous stimulus continues to be received and the ψ tension is restored" (Freud, 1956/1895a, p. 317–318). In other words, the emptiness of the stomach is centrally conveyed and results in an internal state of excitation, of mobilisation of the organism. The newborn child reacts by an undirected motor discharge, in a (vain) attempt to lower the body tension. The baby giggles and screams. Freud (1956/1895a, p. 318) continuous: "The removal of the stimulus is only made possible here by an intervention which for the time being gets rid of the release of $Q\eta$ (excitation quantity) in the interior of the body; and this intervention calls for an alteration in the external world (supply of nourishment, proximity of the sexual object) which, as a *specific action*, can only be brought about in definite ways. At first, the human organism is incapable of bringing about the specific action. It takes place by *extraneous help*, when the attention of an experienced person is drawn to the child's state by discharge along the path of internal state (e.g., by the child's screaming). When the helpful person has performed the work of the specific action in the external world for the helpless one, the latter is in a position, by means of reflex contrivances, immediately to carry out in the interior of this body the activity necessary for removing the endogenous stimulus. The total event then constitutes an *experience of satisfaction* (…)." The mother, or another conspecific, hears the cries and thinks "he must be hungry," she might take the child and put him to her breast. In other words, the mother interprets the cry (or the action) of the child. The child thereby is enabled to release the sucking reflex and milk comes into the body. Thereby, the need is satisfied an this very "removing (of) the endogenous stimulus" is experienced as pleasure according to Freud's (1955/1920, p. 7–8) definition: "We have decided to relate pleasure and unpleasure to the quantity of excitation that is present in the mind but is not in way "bound," and to relate them in such a manner that unpleasure corresponds to an increase in the quantity of excitation and pleasure to a diminution." The milk constitutes an adequate response to the need which was at the source of the discharge impetus (the cry) of the child. Thereby, and thanks to the interpretation, the action acquires a specific status: it becomes an *adequate action* (Freud, 1999/1895b, p. 108).

If the definition of pleasure in this scenario is clear, for Jadin (2012/2009, p. 58), it is also "evident that the endogenous drives (in the experience of satisfaction) constitute an aspect of *jouissance*." Indeed, Lacan (1986/1959–1960, p. 209) considers that jouissance is the satisfaction of a drive, and not simply of the need which is at its origin. Scherrer (2010, p. 143) even adds: "the aim and object of the drive is pure enjoyment, without an object and unconditionally." It is at this point that we would like to propose a first operationalisation of the concepts of pleasure and *jouissance*: indeed, we propose that in Freud's model of the drive ***pleasure is what results from the release of tension induced by the consumption of a suitable object of the drive while jouissance is the (benefit gained from) the motor tension underlying the action which was (once) adequate in bringing relief to the drive.*** In this definition, both, pleasure and *jouissance*, can be aspects of satisfaction of the drive, but, while pleasure implies the consumption of an object, *jouissance* is in the motor mobilization or *use* of the body – i.e., in the motor mobilization of those action pathways that were (once) adequate in delivering pleasure. This definition suits with the juridical origins of the word *jouissance*, where it was reserved for the satisfaction of *using* something without consuming it. Moreover, in the distinction here proposed pleasure is tied to the object, while *jouissance* is related to motor action. This is in agreement with e.g., Marie (2004, p. 27) who says: "*Jouissance* (…) is very close to l'*Agieren*, (…) according to its Latin etymology, agere, i.e., accomplish, express by the movement. Any modality of *jouissance* is of the order of the *Agieren*."

#### *Experience of satisfaction*

The "experience of satisfaction" is a good place to start discussing *jouissance*, e.g., Marie (2004 p. 25) says: "when the question of enjoyment appears in the writings of Freud, in *The Project*, it is about the experience of satisfaction of the drive economy." Let's go back to Freud (1956/1895a, p. 318): "The total event then constitutes an *experience of satisfaction*, which has the most radical results on the development of the individual's functions. For three things occur in the ψ system: (1) a lasting discharge is effected and so the urgency which had produced unpleasure in ω is brought to an end; (2) a cathexis of one (or several) of the neurons which correspond to the perception of an object occurs in the pallium; and (3) at other points of the pallium information arrives of the discharge of the released reflex movement which follows upon the specific action. A facilitation is then formed between these cathexes

and the nuclear neurones." The *pallium*, in Freud's vocabulary, is the part of the central nervous system which is connected with the outer body (specific senses and striated muscles) while the *nuclear* neurons innervate the inner body (the viscera)[1]. Freud (1956/1895a, p. 312) adds that "ω is assumed to be filled from ψ," in other words, it is the ("nucleus" of the) central nervous system which informs ω[2] of the actual values of the homeostatic situation in the inner body.

In other words, the experience of satisfaction is as much the adequate resolve of a drive tension than it is the "radical result" of it, namely a lasting facilitation of the associations between a state of body tension at the level of a neural comparator system (ω), a perceptual image of an adequate object, and a motor representation of an action adequate in resolving the tension. As a result: "(…) when the state of *urgency* or *wishing* re-appears (from ψ to ω), the cathexis will also pass over on to the two memories and will activate them. Probably the mnemic image of the object will be the first to be affected by the *wishful activation.* I do not doubt that in the first instance this wishful activation will produce the same thing as a perception – namely a *hallucination*" (Freud, 1956/1895a, p. 319). We would now add that the wishful activation will also produce a motor body tension, and that this motor tension would then be equivalent to the Lacanian concept of *jouissance.* The biological needs are capable of inducing a reserve of motor tension, which will be recruited to act in order to meet the demands of life, and this reserve of motor tension is equivalent to *jouissance*: "A little bit of *jouissance*, a certain excess is nevertheless necessary from the start. Indeed, the necessities or demands of life (*Not des Lebens*) are such that the nervous system needs to gather a reserve amount to face them" (Jadin, 2012/2009, p. 58).

A question at this point, then, is if this state of body tension is in and by itself in some ways satisfying? It is difficult to decide this question. It could be that body tension has an inherently rewarding effect (see further), but it could also be that the dimension of *enjoyment* more particularly refers to (an) inaugural experience(s) of satisfaction. For example, Scherrer (Freymann et al., 2012, p. 7) says: "The drive is caused by the search, the sting of the recovery of the hallucinatory revival of a previous experience of satisfaction. Hallucination of which we may assume that it was *accompanied by an unprecedented pleasure, particularly intense, excessive, incommensurate with the pleasure associated with the simple release of tension of the need*" (Italics added).

### *Excess of body tension*

For Lacan (1986/1959–1960, p. 42; 1965–1966, p. 137; 1999/1972–1973, p. 26), a body "is something that is made to enjoy, to enjoy itself," "it belongs to a body to enjoy" and "a body is there to be enjoyed." To understand this, let's push the Lacanian understanding of *jouissance* a little bit further. In the inaugural experience of satisfaction of hunger, the baby is given the breast by his mother. In a following frontal encounter with the breast, the sucking movement will be released. Jadin (2012/2009, p. 58–59): "But the case may be that the breast is seen from the side. Discharge, then, is delayed and will only take place after a certain search, for example by means of a movement of the head. For this quest, the child must in a first time decompose the perception, this is the *Urteilen* (…) (the *judging*). The child will perceive at the one hand something identical and specific of the breast, the thing itself of the breast, *the Thing* (*das Ding*) seen from the front, and on the other hand, an element that may vary. When this variable element is strange, the child will delay the discharge. (…) You can see that *the Thing* is something very specific. It is present at the same time when the object satisfying the drive is effectively perceived, and when the object is only imagined as complete, anticipated by desire. *The Thing* is the portion always invested by the *jouissance* (…). In the system of neurons described by Freud that *Thing* of the perceptual complex corresponds to a nuclear neuron of the brain which is continuously invested, continuously filled by endogenous quantities, the production of which is constant."

In our opinion, the notion of jouissance thus seems to balance between two kinds of body tension. The notion of "body tension" is a kind of readiness to act, a motor preparedness, which is probably situated mostly centrally, as an activation level of the central nervous system, but some of which may percolate to the body through subthreshold peripheral motor commands and executions (e.g., mini-contractions). At the one hand, there is the body tension, which we referred to before, specifically preparing an adequate act, which was once accomplished before during an experience of satisfaction. We propose that this part would then correspond to the variable part, as it is activated in reaction to an "attribute" (or an "affordance," in cognitive term; Gibson, 1977)

[1] Note that this roughly corresponds to the divide between the brainstem and limbic system, innervating the vegetative functions of the internal body and the neocortex, innervating the sensory systems and the motor control of the external body.

[2] Freud's ω-neurones are a real headbreaker: they are "excited along with perception" Freud (1956/1895a, p. 309), "behave like organs of perception, and in them we could find no place for a memory" Freud (1956/1895a, p. 309) while "These neurones must have a discharge, however small (…). The discharge will, like all others, go in the direction of motility (…)." Freud (1956/1895a, p. 311). Freud (1956/1895a, p. 309) *needs* to think them to understand how physical entities (e.g., stimuli), which structurally are *quantities*, become mental entities characterized by *quality.* As to their working principle, Freud proposed that they are incapable of receiving stimuli, "but that instead they appropriate the *period* of excitation and that this state of theirs of being affected by period while they are filled with the minimum of *Q*η [quantities, stimuli] is the fundamental basis of consciousness" Freud (1956/1895a, p. 311) and indeed "consciousness is the subjective side of one part of the physical processes in the nervous system, namely of the ω processes." We propose that these ω-neurones could stand for *comparator systems* in general, which very much work like thermostats comparing set-values with actual values (see also Bazan, 2007). They allow absolute quantity amount to acquire, by comparison, value labels (e.g., "so much short of," "so much in excess of," etc.), i.e., *they transform quantities in qualities.* The confusion about them being sensory or motor would be logical as they comprise a sensory monitoring directly connected to a possible (disinhibition of) discharge. Moreover, Freud adds: "*unpleasure* would have to be regarded as coinciding with a raising of the level of *Q*η or an increasing quantitative pressure; it would be the ω sensation when there is an increase of *Q*η in ψ. Pleasure would be the sensation of discharge." We are tempted to translate this as follows: at the level of the comparator the more the set value and the actual value differ, the more this is unpleasurable, while when they coincide, there is discharge and, consequently, relief, which is pleasurable. And then: "Pleasure and unpleasure would be the sensations in ω of its own cathexis, of its own level; and here ω and ψ would, as it were, represent intercommunicating vessels. In this manner the quantitative processes in ψ too would reach consciousness, once more as qualities" (Freud, 1956/1895a, p. 312). The idea of "intercommunicating vessels" could fit with these comparator systems which are, indeed, continuously balancing neurons firing for target values (e.g., efference copies) and afferent information which has already gone through ψ, the central nervous system. The cryptic "period" which Freud refers to, could tentatively be understood as the intensity of firing of the one and the other type of neurons, i.e., at the level of the neural comparator systems the only point which still matters is to balance out the intensity levels of both informations.

which functions as a handle for manipulation of the object; as a consequence, it can be represented. At the other hand, there is the body tension, which is induced by the constant "and specific" part of the object, the essence of the thing, *das Ding* itself, which allows it to be identified as such even if the usual attributes for grasping it have changed. What we propose goes as follows: ***as the thing is identified*** – i.e., identified from a past experience of satisfaction, as a potentially satisfying object – ***it induces body tension, which will be needed to act upon it, but*** as the usual "handles" have changed, ***this body tension is yet without clear motor execution form.*** We could say that it has not yet moved (very far) to the motor discharge part of the mental apparatus. Probably this second reading of *jouissance* is closer to Lacan's (1986/1959–1960) concept of "enjoyment of the Thing." Jadin (2012/2009, p. 38) says that Lacan presents *jouissance* "in some ways as this which resists to attribution[3]" and further on he adds: "*Jouissance*, the Thing, is thus that which precedes a certain manipulation. It dates from (the time) before the hand" (Jadin, 2012/2009, p. 50). It is (more) easily understood, then, why this jouissance is considered "out-of-representation" (see also Hoffmann, 2012/2009, p. 9): the reserve of body tension has not yet been destined to a determined motor form, which is the basis for representation (see further). Perhaps we could also say it is still very much biological, and not yet mental?

We should also consider the possibility that it is only in this second scenario that, by chance or by surprise, finding the "adequate" way to grasp the object will be "accompanied by an unprecedented pleasure, particularly intense, excessive, incommensurate with the pleasure associated with the simple release of tension of the need," and that this is what specifically underlies the powerfully satisfying dimension of *jouissance*. But maybe, once found, a new share of body tension shifts to the mental side, where it can be represented. However, the successful mobilization of this share of body tension, though it will be activated at a new encounter with *the Thing*, won't be able to induce the same extent of gratification as the first time. But at the other hand, if a pathway of discharge is not found, tension may accumulate and this, then, might lead to the experience of pain. Freud (1955/1920, p. 63) says: "Our consciousness communicates to us feelings from within not only of pleasure and unpleasure but also ***of a peculiar tension*** *which in its turn can be either pleasurable or unpleasurable*" (Italics added). Indeed "*jouissance* is suffering" (Lacan, 1986/1959–1960, p. 185) and "What I call *jouissance* – in the sense in which the body experiences itself – ***is always in the nature of tension***, in the nature of a forcing, of a spending, even of an exploit. Unquestionably, there is *jouissance* at the level at which pain begins to appear, and we know that it is only at this level of pain that a whole dimension of the organism, which would otherwise remain veiled, can be experienced" (Lacan, 1966–1967, p. 60; Italics added). We see now also how the pleasure principle thus functions as "a limit to enjoyment" (Lacan, 1991/1969–1970) when it discharges shares of the body tension, bringing relief, and thus pleasure, and limiting the amount of (painful) *jouissance* tension.

## HISTORY

### *Commemoration of a trait, complying to repeat*

The radical result of the experience of satisfaction is a facilitation or memory trace "between two mnemic images and the nuclear neurones which are cathected in the state of urgency" (Freud, 1956/1895a, p. 319)[4] . It is the cathexis of the nuclear neurones (which coming from ψ fills ω) which induces a facilitation between the mnemic image of the satisfying object and the (once) adequate motor act. When Freud (1949/1905) says in: "This satisfaction (of a drive) must have been previously experienced in order *to have left behind a need for its repetition*; and we may expect that *Nature will have made safe provisions so that this experience of satisfaction shall not be left to chance*" (Freud, 1949/1905, p. 184; Italics added), we may assume that these "provisions" minimally entail the described inscription of the memory traces. But these are not just passive traces: indeed, they "leave behind a need for their repetition." Freud (1955/1920, p. 42) explains how this goes in *Beyond the pleasure principle*: "The repressed instinct never ceases to strive for complete satisfaction, which would consist in the repetition of a primary experience of satisfaction (…) it is the difference in amount between the pleasure of satisfaction which is demanded and that which is actually achieved that provides the driving factor[5] which will permit of no halting at any position attained, but, in the poet's words, "ungebändigt immer vorwärts dringt'.[6]" In other words, the traces are not simply sitting there but are continuously activated by the insisting incoming stream from the source of the drive.

Lacan (1991/1969–1970, p. 111–112) comments: "In 1920, what Freud is dealing with in the exploration of the unconscious, is repetition[7]. (…) Repetition is the denoting, the precise denotation of a trait (…) being identical to the unary trait, to the little stroke, to the element of writing, of a trait in so far as it commemorates an irruption of enjoyment." Freud (1949/1905, p. 1212) says, speaking about thumb sucking, that the child is "is determined by a search for some pleasure[8] which has already been experienced and is now remembered." Repetition, thus, is the commemoration of

[3]"Referring to the two judgments which must be applied toward a thing, the judgment of existence and the judgment of attribution, Freud holds that one can assign an infinite number of attributes to a thing, to *The Thing*, to the *ousia*. When Lacan argues that *jouissance* is *ousia*, he presents it in some ways as this which resists to attribution, as that which is excluded from the attribution judgment (…)."

[4]Freud explains a mechanism of how such a memory trace may come about: "Now there is a basic law of *association by simultaneity*, which operates in the case of pure ψ activity, of reproductive remembering, and which is the foundation of all links between the ψ neurones. We find that (…) *quantitative cathexis of a ψ neurone, α, passes over to another, β, if α and β have at some time been simultaneously cathected* from Φ (or from elsewhere) [Italics added]. Thus *a contact-barrier has been facilitated through the simultaneous cathexis α–β*." – with Φ, being the "permeable" neurones at the periphery of the mental apparatus, both perceptual or motor neurones. Note that Freud's description is equivalent to Hebb's (1949) law and explains how the easy connexion between two neurones comes about by being first both simultaneously activated from elsewhere.

[5]Freud seems to allude to the idea that this incoming stream is compared with a set value in a comparator type monitoring mechanism such as what we have proposed for ω.

[6]"Presses ever forward unsubdued." Mephistopheles in *Faust*, Part 1 [Scene 4].

[7]Our translation of "En 1920, ce à quoi Freud a affaire dans l'exploration de l'inconscient, c'est la répétition." Which we prefer above the official translation which is "This is even what Freud discovered precisely around 1920."

[8]This pleasure here is *jouissance*, the enjoyment of the body tension which was once adequate in bringing pleasure.

an irruption of enjoyment. Lacan (1986/1959–1960, p. 209): "the drive as such is something extremely complex (…) It embodies a historical dimension whose true significance needs to be appreciated by us. This historical tendency is defined by this, by *this mark, consisting of the drive presenting itself with a certain insistence, in its status of referring* to something memorable because it was remembered[9]. Remembering, "historicizing," is coextensive with the functioning of the drive in the human psyche." We can read here the reference to Freud's facilitation induced by the drive between the two mnemic images, brought about by the experience of satisfaction. This coupling of events forms *a trait or a mark*, commemorating an irruption of enjoyment, and inducing a relentless tendency to repeat: "The compulsion to repeat and (drive) satisfaction which is immediately pleasurable seem to converge here into an intimate partnership" (Freud, 1955/1920, p. 23).

Therefore, taking all this together, we are inclined to think that the experience of satisfaction, having been in itself an experience of *jouissance*, leaves behind a powerful memory trace, which will be readily activated whenever a similar body need or drive situation is aroused, or when "the Thing" is reencountered, thereby inducing a reactivation of the memory images of this (once) satisfying object as well as of the (once) satisfying action. This reactivation will bring about in and by itself *jouissance* through motor tension. This tension might procure (some) enjoyment, especially if some new motor pathway to approach the object has been thought out. Remarkably, this enjoyment then will be released quite independently of the object and action still satisfying the drive from which they historically originated.

## PHYSIOLOGY: THE DOPAMINERGIC PATHWAYS

### BODY

#### *Model of the drive: mobilise the external body from within*

In the natural history of life, it is with the first vertebrates 520 million years ago that the striated, or *voluntary*, muscles emerge as the system to move the newly invented internal skeleton (see also Bazan, 2008). Vertebrates, then, are schematically constituted of two bodies: an internal body, the invertebrate body, consisting of the so-called vegetative systems for blood circulation, respiration, digestion, excretion, sudation, reproduction etc., and an external body, consisting of the skeleton and the striated or skeletal muscles. These bodies having been in some ways superposed the one upon the other in the course of evolution, for the organism to function efficiently, there must be a system that adjusts the signalling of internal body needs (e.g., oxygen, food, hydration, sex objects) to specific actions of the external body which can alleviate these body needs.

A first physiologic understanding of the Freudian concept of the drive, then, would be the dynamics whereby a body tension, originating from a need in the internal body, mobilises the external body and instigates it to action. One key hypothesis then is that *central dopaminergic systems* could embody the physiological architecture of Freud's concept of the drive. In the striatum, dopamine (DA) serves as a critical motor action signal; increases in DA are associated with increases in motor output, and decreases in DA with inhibition of behavior. In the case of the mesolimbic pathway, the ventral tegmental area (VTA) innervates the nucleus accumbens shell (NAS), which is part of the corpus striata (basal ganglia); this system is therefore referred to as NAS-DA. This is also the so-called SEEKING *system* of which the neuroscientist Panksepp (1998, p. 145; 144) says that when this system is stimulated: "organisms deploy *the most energized exploratory and search behaviors an animal is capable of exhibiting*: e.g., stimulated rats move about excitedly, sniffing vigorously, pausing at times to investigate various nooks and crannies of their environment," or else: "The desires and aspirations of the human heart are endless. (…) But they all come to a standstill if certain brain systems, such as the DA circuits arising from midbrain nuclei are destroyed. (...) These circuits appear to be major contributors to our feelings of engagement and excitement as we seek the material resources needed for bodily survival. (...) Without the synaptic "energy" of DA these potentials remain dormant and still. (...) When DA synapses are active in abundance, a person feels as if he or she can do anything."

The psychoanalyst and neuroscientific researcher Howard Shevrin has previously made a convincing case that Panksepp's SEEKING system could stand as a physiological correlate of Freud's concept of the drive (Shevrin, 2003). Shevrin (2003) indicates how the four parts of the SEEKING system are remarkably similar to the four parts of Freud's definition of drive and proposes to illustrate this with a simple table (**Table 1**).

Indeed, Panksepp's SEEKING system is made up of four parts: regulatory imbalances, consummation, external stimulus, and powerful states of expectancy or anticipation, while Freud's architecture of the drive is also made of four parts. Shevrin (2003) proposes the following parallels: the regulatory imbalances in Panksepp's model are the underlying specific need states such as hunger, thirst, and sex; thus they correspond with the somatic source of the drive. Consummation refers to the satisfying of the underlying need state, which is what corresponds to the aim of the Freudian drive. External stimulus refers to the object providing the consummatory satisfaction, the most variable component. Concerning the fourth component, Panksepp's "powerful states of expectancy or anticipation," they refer to the activation of the NAS-DA. According to Panksepp (1998, p. 145),

**Table 1 | Shevrin's (2003) proposition of the parallels between the four parts of Panksepp's SEEKING system and the four parts of Freud's definition of the drive.**

| Panksepp's SEEKING system | Freud's drive theory |
|---|---|
| Regulatory imbalances | Somatic source (*Quelle*) |
| Consummation | Aim (*Ziel*) |
| External stimulus | Object (*Objekt*) |
| Energetic activity | Motor factor (Drang) |

[9]Our translation of "Cette tendance historique se définit en ceci, dans cette marque que la pulsion se présente dans une certaine insistance, en tant qu'elle se rapporte à quelque chose de mémorable parce que mémorisé." which we prefer above the official translation which is "This dimension is to be noted in the insistence that characterizes its appearances; it refers back to something memorable because it was remembered."

activation of this system is characterized by a "psychic energization." When it is activated "…animals perform a large number of motivated goal-seeking behaviors. If this system is damaged, a generalized behavioral inertia results" (Panksepp, 1998, p. 150). Shevrin (2003) indicates that Panksepp's inference concerning the subjective state of the animal when the NAS-DA circuits is activated, "is based on the intense motor activity of the animal engaging in exploratory activity. In other words the animal is according to Panksepp, energetically active. This clearly implicates a motor factor. Moreover, the activation of the NAS-DA circuits results in an animal engaging in effortful behavior, in Freud's terms, a demand for work is being made in the most basic meaning of the word work." In this sense, the "powerful states or expectancy or anticipation" also correspond quite precisely to Freud's component of motor pressure. We therefore propose that the functioning of the (mesolimbic) dopaminergic pathways could embody a physiological counterpart of Freud's drive concept[10].

Let's again take the case of hunger. Indeed, Panksepp (1998, p. 167) states: "The SEEKING system, under the guidance of various regulatory imbalances, external incentive cues and past learning, helps take thirsty animals to water, cold animals to warmth, hungry animals to food, and sexually aroused animals toward opportunities for orgasmic gratification." However, if we want to apply this model to the "simple" situation of a hungry baby crying for food the first time, we run into an endless series of complications. First, there are many redundant mechanisms to ensure adequate food consumption any of which may be sufficient to stimulate food intake. Second, the pathways from the internal homeostatic receptor systems detecting various bodily imbalances and inducing the activation of the SEEKING system, i.e., inducing DA-release, are multiple. It is beyond our goal and expertise to give an overview of these, but it seems that the brain architecture underlying appetitive motivation is generally compatible with a drive concept embodied by dopaminergic transmission. For example, if we want to go from hunger to the mobilisation of the external body, the hypothalamus seems a good place to start. It is well established that the arcuate nucleus of the hypothalamus receives humoral signals, both from various nutrients and from various hormones, regarding the status of peripheral energy stores and conveys this information to the lateral hypothalamic area (Elmquist et al., 1999). The LH influences voluntary somatic motor systems governing complex food-searching and food-related behavior. If the LH is activated and food is not present, animals act very aroused, are hyperactive, and appear to engage in searching or foraging behavior (Kelley et al., 2005a,b). Moreover, this LH involvement seems to imply dopaminergic pathways. The lateral hypothalamic corridor between the LH and the VTA is part of the Medial Forebrain Bundle which runs from the VTA to the NAS. The LH also has direct connections with the accumbens shell giving the NAS a privileged access to hypothalamic energy-sensing substrates; however, the LH also more directly reaches widespread areas of striatum (beyond the accumbens) via midline thalamic projection (for review, see Kelley et al., 2005a). In other words, dopaminergic innervation of the striatum, both ventral and dorsal, is involved in food intake, and this system is concerned with motor activation and foraging strategies associated with changing motivational conditions (Haberny et al., 2004; Haberny and Carr, 2005). The complexity of these pathways, however, is huge and there are discrepant opinions in different authors[11]. What is important in the present exercise, is not to show that the dopaminergic transmission is a *necessary* condition for the engagement in appetitive behavior, but to show that the architecture of the brain is broadly *compatible* with the drive mechanism as embodied by dopaminergic transmission, i.e., that it is a possible pathway. Indeed, the first experience of satisfaction, the first cry of the hungry baby may have a quite different physiology as the adult "routine" hunger usually studied in neurosciences. Concretely, when Freud indicates that "The nucleus of $\psi$ is connected with the paths by which endogenous quantities of excitation ascend. (…) The filling of the nuclear neurones in $\psi$ will have as its result an effort to discharge, an urgency which is released along the motor pathway," it seems that, given the data summarised above, we are in a position to propose to translate this as: "the central dopaminergic systems are connected with paths which convey information of the internal homeostatic situation of the body, e.g., through the LH. Ascending excitations, indicating, e.g., a food depletion centrally, will lead to release of DA, which will lead to motor mobilisation."

But how can we now situate the proposed difference between pleasure and *jouissance* in this physiological model? Shevrin (2003) underlines that it has been established across many animal species that once an animal is conditioned to expect a reward following the appearance of a conditioned stimulus such as a light, that at a certain point it will begin to treat the light as if it were the reward itself, in particular if no reward has been forthcoming. A pigeon, for example, will begin to peck at the light even though its pecking has nothing whatsoever to do with the appearance of the reward. This phenomenon is called autoshaping, that is, says Shevrin (2003) "*the animal's own response, the pecking, becomes intrinsically rewarding.*" When the NAS-DA circuit is artificially blocked with antagonists, the autoshaping disappears (e.g., Di Ciano et al., 2001). Shevrin (2003) comments: "(...) it is not the anticipation of some consummatory pleasure that is involved, a totally different matter, but a pleasure of some sort intrinsic to drive activation. *Consummatory pleasure and, if I may call it that, drive pleasure are two different things.* The first I submit is an emotion or affect in the usual sense; *the second is a unique state of expectation or anticipation that is intrinsically gratifying, but not pleasurable in the usual sense. It is entirely expressed through action,*

[10]Other neuroscientific authors have also made propositions in the same line, though probably not with *Freud*'s concept of the drive in mind: e.g., Kupfermann et al. (2000, p. 998) in their seminal work *Principles of neural science* propose that the mesolimbic DA transmission appears to represent a state of motivation or drive wherein drive states can be understood as a state of tension due to a physiological need or homeostatic imbalance. Drives direct behavior toward a goal, able to reinstall homeostasis via consumption of an object (e.g., food). Moreover, they increase general alertness, energizing an individual to act appropriately in a given situation, in order to obtain a goal.

[11]For example, even if a specific role for the medial accumbens shell in food-directed behavior and food consumption was indeed demonstrated (Stratford and Kelley, 1997; Reynolds and Berridge, 2001), Kelley et al. (2005a) sums up a number of results which seem difficult to reconcile with the idea that dopaminergic transmission is necessary for appetitive approach.

*rather than accompanying action* as is the case with consummatory pleasure[12]" [Italics added]. Shevrin's concept of *consummatory pleasure* seems to parallel Freud's concept of *pleasure*, resulting from the release of tension induced by the consumption of a "suitable" object (of the drive). Shevrin's difference between consummatory and drive pleasure therefore parallels quite nicely our own distinction between pleasure and *jouissance*, with *jouissance* defined as the benefit gained from the motor tension underlying the action brought about by the drive, and it allows us to situate the concept of *jouissance* at the level of the intrinsic NAS-DA activation.

These distinctions are also in a remarkable resonance with another neuroscientific distinction. Indeed Berridge (1996), as well as Robinson and Berridge (1993, 2000, 2003), propose a distinction between *wanting* and *liking*. It was first these author's merit to master two different ways of measuring appreciation in rats: at the one hand, the hedonic (*liking*) or aversive reactions are measured on the basis of facial reactions (some of which are conserved over different species); at the other hand the *wanting* is measured on the basis of the amount of motor activation which the organism is ready to invest in order to obtain the reward. These distinctive parameters allowed for the dissociation of two anatomical circuits (Berridge, 1996): the *wanting* circuit corresponds with the mesolimbic NAS-DA of Panksepp's SEEKING system, the *liking* circuit corresponds with so-called "opioid hotspots," involving among others the shell of the nucleus accumbens, the ventral pallidum and the parabrachial nucleus of the pons in the brain stem. These circuits function independently of each other. For example, considerable research with the taste reactivity test has demonstrated that interference with DA failed to alter appetitive taste reactivity for sucrose (Berridge and Robinson, 1998). Also, enhancing DA neurotransmission is not sufficient to produce pleasurable subjective effects in humans (Rothman and Glowa, 1995). This has led Robinson and Berridge (1993) to conclude that, though the original hypothesis emphasized the role that pleasure played in mediating the effects of dopaminergic manipulations, brain DA does not mediate *liking*. Nevertheless, DA systems are involved in *wanting* of natural and drug reward (see Berridge, 2007); this *wanting* is determined by the intensification of the *wanting* circuits quite independently of *liking*. Indeed, work of these authors shows that activation of DA systems enables or increases behavioral responses necessary for obtaining a goal object, while interference with DA potently affects the willingness of the animal to engage in behavioral actions aimed at anticipating or foraging for food (e.g., Berridge, 1996). It is therefore tempting to draw a parallel between these physiological findings and the psychoanalytic concepts: Berridge's *wanting* and the psychoanalytic concept of the drive bear some similarities for as far as they both concern the readiness to engage in a motor behavioral effort[13].

In summary, the proposition that the *central dopaminergic systems*, and in particular the NAS-DA system, could embody a physiological counterpart of the psychoanalytic concept of *jouissance*, seems to be coherent both with the drive-dimension of jouissance and with an understanding of *jouissance* as the benefit gained from the motor tension underlying the action which was (once) adequate in bringing relief to the drive, as Shevrin points out with the phenomenon of e.g., autoshaping. Furthermore, through Shevrin's distinction between consummatory and drive pleasure, we can see how the Lacanian distinction between pleasure and *jouissance* might reflect or parallel a number of exclusively neuroscience-based distinction, as well as, prominently, the distinction between *liking* and *wanting*.

### *Experience of satisfaction: tag the action associated to a reward*

A second aspect of the *jouissance*-NAS-DA convergence would be a convergence around some way of marking the adequate act. The psychoanalytic idea would be that the adequate act, which is also pleasurable, gets is some ways "tagged" during the experience of satisfaction and we have proposed that it is this tagging by experience that will readily reactivate the specific motor pattern when a comparable situation of need is measured by the ω-neurones. The reactivation of this body tension was tentatively understood as *jouissance*. Now, it is well characterised that the presentation of a rewarding stimulus, whose reward value cannot be anticipated, produces a burst of DA firing (Bromberg-Martin et al., 2010). This could fit the psychoanalytic model if some conditions are met. First, the idea of reward should also (partially) cover the Freudian dimension of pleasure, in the sense that the rewarding stimulus should procure tension relief, in particular by being an adequate response to a bodily imbalance situation. Second, it is then this pleasure which should induce the DA release. Third, the effect of this DA should (also) be on the level of the actions involved by stimulus rather than (exclusively) on the stimulus itself and in some ways tag these actions so as to distinguish them from other actions.

First, is the "reward" of the physiological observations comparable to the Freudian pleasure? Salamone et al. (2007, p. 462) define reward as a positive reinforcer with emotional effects, such as

[12] Interestingly, Salamone et al. (2007, p. 465) summarize in a footnote a number of comparable distinctions which several authors have made between two kinds of gratifications: e.g., activational versus directional; preparatory versus consummatory; instrumental versus consummatory; anticipatory versus consummatory; ethanol seeking versus ethanol intake; anticipatory versus hedonic.

[13] Similarly, Robinson and Berridge's *liking* and the psychoanalytic concept of *pleasure* bear some similarities for as far as they both concern a pleasure or hedonic experience upon consummation of an object. However, *pleasure* in the Freudian sense is defined as a relief of body tension due to the satisfaction of a bodily need. *Liking*, at the other hand, is brought about by stimulation of the opioid hot-spots which react by innate pathways to the "orosensory properties" (i.e., its sweet taste and fatty flavors), to some extent independently from the information on the homeostatic situation of the internal body (Sclafani, 2004). Of course, this schema works for as long as we stick with "basic" drives which are so fundamental to life and conserved over evolution that they have strong innate foundations. But there are many other internal body tensions which can arise in the course of our first interactions with our primary caregivers besides hunger, especially in the human species – which of all species is the most dependent of his first caregivers. It would be interesting to find out if homeostatic relief, in general, can lead to opioid activation and if this opioid activation could serve as a criterion for the dopaminergic tagging of the associated action. Different elements point in that direction, since, e.g., the homeostatic state can modulate the rewarding value of a stimulus, but the total picture remains unclear. Now, for the model to function beyond more innate drives like hunger (where associated criteria like sweetness may suffice as a criterion for the adequacy of action), i.e., for the model to function in more typically human situations, the dopaminergic reward system should be able to take into account the situation of the internal body as a criterion for tagging actions. In this sense the NAS-DA being informed of this homeostatic information is sufficient (see further) and the opioid activation may or may not constitute a correlate of the Freudian concept of pleasure.

feelings of pleasure. The term reinforcer goes back to Thorndike's (1911) "Law of Effect" which says that "any act which in a given situation produces satisfaction becomes associated with that situation so that when the situation recurs the act is more likely than before to recur also." This is basically the same as what Freud says for the experience of satisfaction, but Freud gives a criterion for pleasure: he refers to a lasting discharge the information of which is conveyed by the ω neurones, which are filled with the (subcortical and brainstem) neurones in connection with the internal body. So, yes, there is some equivalence between the Freudian concept of "pleasure" and the cognitive concept of "reward" with this proviso that in the cognitive concept no concrete criterion for "satisfaction" is included.

Second, is it then this pleasure which induces the DA release? The neuroscience findings show that it is only when the reward is unexpected that there is a burst of DA firing (Schultz, 1998). So, (Freudian) pleasure does not *per se* lead to DA release, but can it in principle do so, e.g., at some inaugural occasion or in some important need situation? Food in a hungry animal is a very strong reward, but it is probable that here a number of innate criteria (e.g., sweetness) are the triggers for the DA release, and not essentially the relief of the inner body imbalance. However, DA can signal the salience of a variety of potential reward and reward-related cues (Schultz, 1998) and DA appears to play a broad role in motor behavior, rather than a specific role in food intake (Verty et al., 2004; Kelley et al., 2005b). If so, there must be a mechanism beyond the innate which function as a criterion for DA release. It remains unclear how strong, e.g., the role for homeostatic cues of the internal body is in the triggering of DA release, but a contribution of this mechanism is probable given the modulatory role of e.g., satiety on DA release, and should play a more important role for acquired action pathways to find pleasure, or to avoid unpleasure, in complex unanticipable (human) situations.

Now, when encountering such an unexpected reward, DA neurons often produce phasic bursts of activity including multiple spikes (Schultz, 1998). Strikingly, these phasic bursts, which are in this moment perceived as pleasurable (Bromberg-Martin et al., 2010), could be some physiological counterpart of the dimension of *enjoyment* which we have attributed especially to the *inaugural* experience of satisfaction, "*an unprecedented pleasure, particularly intense, excessive, incommensurate with the pleasure associated with the simple release of tension of the need.*" The pleasure here is not to be understood in the Freudian sense, since, indeed, DA and accumbens neurons do not discharge during actual consumption of an expected reward, when the most pleasure is presumably experienced (Schultz, 1992, 1998). It is another kind of pleasure, namely *jouissance*. Strikingly, we are reminded of Freud's (1955/1920, p. 35) words: "Novelty is always the condition of enjoyment."

Thus, DA neuron responses are not triggered by reward consumption *per se*, except if the reward was unexpected. Instead, DA neurons discharge *in anticipation of reward* (Koob and Volkow, 2010). Indeed, DA neurons are excited when a cue indicates an increase in future reward value. Alluding to the higher described phenomena of auto-shaping, Volkow et al. (2012, p. 9–10) say that "the mere prediction of a reward may eventually become the reward (…) this type of functional "switch" has also been reported for natural reinforcers, which are likely to induce an equivalent and gradual shift in DA increases (…) in the transition from a novel stimulus that is inherently rewarding to that of the associated cues that predict it[14]." Berridge and Robinson (1998) propose that the phasic DA-bursts *create a state of motivation to seek reward* (see also Salamone et al., 2007). They motivate the individual to obtain the hedonic reward "so that the individual almost cannot sit still" (Berridge, 2007, p. 408). This DA release is necessary for reward cues to cause an increase in general motivation to perform reward-seeking actions (Bromberg-Martin et al., 2010, p. 15). Knutson et al. (2001, p. 271) suggest that the nucleus accumbens "may provide the motivational "engine" that fuels attainment of immediate reward." This characteristic of behavior has enormous adaptive significance because it enables organisms to exert effort to overcome obstacles or work-related response costs that separate them from biologically relevant stimuli (Van den Bos et al., 2006). We are tempted to make some parallel here between these diverse neuroscience interpretations and Jadin's (2012/2009, p. 58) psychoanalytic "little bit of *jouissance*" which is nevertheless necessary to face the "demands of life (*Not des Lebens*)" which are such "that the nervous system needs to gather a reserve amount to face them." In this light, it is interesting to stress that DA systems are activated not only by positive stimuli, but also by aversive, painful and stressful stimuli and events (Berridge and Robinson, 1998; Salamone et al., 2007). Indeed, both rewarding and aversive situations require an increase in general motivation to energize actions and to ensure that they are executed properly. This fits with the clinical observation that *jouissance* can also be tied to actions which were (once) adequate not simply in obtaining pleasure (rewarding situations) but also in avoiding displeasure (aversive situations).

This brings an answer to our third point, namely that the effect of the DA is (also) on the level of the actions involved by the stimulus rather than (exclusively) on the stimulus itself. When Bromberg-Martin et al. (2010, p. 8) say that DA neurons are critical in motivating effort to achieve high-value goals, he adds "and (in) translating knowledge of task demands into reliable *motor performance*." As a result, the organism will search the stimulus and "*learn actions* to seek it again in the future" (our Italics). Furthermore, Berridge (2007, p. 408) proposes that the DA *tags* the unexpectedly rewarding actions with "incentive value," which "is a separate form of value added to neural representations of learned signals that predict hedonic reward and which translates the mere prediction into motivation. Incentive salience attribution makes a specific associated stimulus or action into an object of desire[15] and can tag a specific behavior as the rewarded response the individual is motivated to perform." Representations of motor processes and cognitive processes are put into chunks in order to mark events

[14]This transition is conveyed through DA signalling, which appears to code for a so-called "reward prediction error," which has been proposed to act as a teaching signal that underlies reinforcement learning (Schultz, 1998). However, Berridge (2007), on the basis of a series of empirical observations, refutes the causal role of DA in (reinforcement) learning and proposes that, in order to explain why mesolimbic dopamine neurons so elegantly fire seemingly obeying prediction error equations, they code an informational *consequence* of learning signals, *reflecting* learning and prediction generated elsewhere in the brain rather than causing it. Salamone et al. (2007) also distinguish a possible role for DA in learning from its motivational or reward role.

[15]We can't help but point out that even Berridge's word choices become properly psychoanalytic at times.

as salient and induce appropriate action patterns (Salamone et al., 2007). Although the neural mechanisms of priming are not fully known, "generation of incentive salience is the dynamic process for which mesolimbic DA neurotransmission may be most essential" (Berridge, 2007, p. 412).

Taking all this together, we think we have reasons to see parallels between Freud's experience of satisfaction and the dopaminergic attribution of incentive salience to reward-related actions. A distinctive feature between the Freudian model and the DA models is that in the Freudian model the instigation (for motor activation) is more readily understood as coming from within the organism, originating, e.g., from some homeostatic imbalance situation, pushing to go find reward, while in the DA models the instigation is induced by some perceived stimulus, potentially announcing a reward. However, one could conceive of both models as three-way connexions both implying all three, the bodily need, the perceived stimulus or object[16], and the motor pathway to grasp it or interact with it. Indeed, Berridge (2007, p. 414, 413) states it as follows: "the mesocorticolimbic circuitry (…) mediates the integration of learned signals with hunger/satiety states to dynamically transform the motivational value of stimuli" or even more directly: "physiological deprivation states (…) motivate and direct (behavior) chiefly by enhancing the motivational and hedonic values of their relevant external incentive stimuli and that is a function for which mesolimbic mechanisms may be important."

This last sentence resonates with "when the state of urgency or wishing re-appears, the cathexis will also pass over on to the two memories and will activate them," the two memories being the rewarding object or incentive stimulus and the motor pattern of its associated behavior. As indicated, the precise role of DA release in this dynamic is to fuel the organism by creating a state of motivation to seek reward, and this again is strikingly close to the definition of *jouissance* we have proposed in the framework of the experience of satisfaction, namely the motor body tension instigated by the wishful activation. We can also hear quite directly the neuroscience connexion between reward and motivation in Freud's (1955/1920 p. 23) statement: "The compulsion to repeat and (drive) satisfaction which is immediately pleasurable seem to converge here into an intimate partnership."

### *Excess of body tension: induce excess to the point of exhaustion*

If *jouissance* is to be understood as equivalent to a state of motor activation, then, by consequence, it is also equivalent to an increase in body tension. Indeed, any action intention, be this action actually executed, or simply imagined, remembered, prepared, anticipated or even prevented (e.g., Jeannerod and Decety, 1995; Decety, 1996; Gallese, 2000), leads to a slight increase in muscle tension (ex. Yue and Cole, 1992). The actions which are actually executed are only a fragment of all motor activations continuously mobilising the body and causing muscle tension. The idea of *jouissance* as (the benefit from) a state of motor activation, therefore leads us directly, following a physiological logic, to the idea of sustained high levels of body tension, corresponding to what seems to be put forward by Lacan as central in the concept of *jouissance*, namely the implication of the body.

What then about Lacan's proposition of the closeness between *jouissance* and the notions of excess and pain? It is interesting, in this respect, to remember the first observations implying the stimulation of the nucleus accumbens. Indeed, in a well-known series of experiments, Olds and Milner (1954) devised a system enabling a rat to stimulate its own brain, by means of a lever connected to an electrode implanted in the forebrain. Olds and Milner (1954) describe that rats would continually press the lever in return for receiving nothing more than a brief pulse of electrical stimulation. It turned out that a similar effect was also produced when the electrodes were implanted in the nearby nucleus accumbens (Olds, 1956). The rats would press the lever frequently to receive stimulation and would work so vigorously to self-administer stimulations to the point of exhaustion and the exclusion of all other activities (e.g., eating drinking, sex, and sleep). When, in the wake of certain surgical procedures, similar stimulations were possible for some human patients, it was indeed also observed that these patients preferred this self-stimulation above all other activities. But, curiously, this stimulation was not associated with any external sign of pleasure: no smile or relaxed face, or any other sign of tangible happiness, or subjective expression of a pleasant sensation (Berridge and Kringelbach, 2008, p. 15). It is for this reason then that the term "reward" circuit was chosen rather than Olds and Milner's (1954) first description of "pleasure center." What is moreover striking is that is again the same neurophysiologic axis, the NAS-DA, which is implied here and that it reveals itself as an axis which could, if circumvented (or "perverted;" ex. by self-stimulation), easily lead to excess to the point of exhaustion and self-harm.

To further strengthen this idea that the same mechanism, so vitally important in driving the organism and in tagging adequate actions, is also the mechanism which easily shifts toward harmful effects, let's go back to the role of the NAS-DA in inducing body tension. Indeed, the situation of self-stimulation is artificial and therefore not common. However, let's remember that DA is not generally released during the consummatory phase, but in advance of it, inducing a state of motor tension leading the organism to move toward the rewarding stimulus. In that sense it is interesting to note that, e.g., Kupfermann et al. (2000) comment that this anticipation, or motor tension, translated by the mesolimbic DA firing, can be interpreted as a deficit, inducing *an anxiogenic state of tension*, rather than being already rewarding *per se*. For all these reasons, we contend to say that in the same way as for *jouissance* where the boundary between enjoyment and pain seems flimsy, the mesolimbic NAS-DA functioning might be so built that it is in a constant instable balancing between reward and anxiety. Moreover, in both cases it is the part of the body tension which actually can go into effectively executed action, and therefore into discharge, which limits the build-up of tension, and therefore of pain or anxiety. This then could be some physiological counterpart of the psychoanalytic idea of pleasure functioning as a limit to *jouissance* (Lacan, 1991/1969–1970).

[16] which would be "the Thing" in the psychoanalytic reading, see Excess of Body Tension: "as the thing is identified – i.e., identified from a past experience of satisfaction, as a potentially satisfying object – it induces body tension, which will be needed to act upon it."

## HISTORY

### *Commemoration of a trait, complying to repeat: incentive sensitization*

As concerns the history dimension of *jouissance*, we will elaborate on Robinson and Berridge's "incentive sensitization" theory since this theory not only entails the tagging effect of DA release but more specifically the *structural* inscription aspects of the DA reward system and therefore seems to be in an ideal position to translate the specifically *historical* dimension of *jouissance*. Indeed, when Robinson and Berridge first present their incentive sensitization theory of addiction in 1993, they proposed that the most important of the psychological changes in addiction is a "sensitization" or hypersensitivity, i.e., *long-lasting adaptations* in the mesolimbic NAS-DA. Addictive drugs share the ability to produce persistent neuroadaptations that render these regions hypersensitive. The data suggest that sensitization may involve more than a simple up- or down-regulation of biochemical processes, but it may involve changes in patterns of synaptic connectivity in brain reward systems, changes that may be similar to those seen in other neural systems in association with other forms of experience dependent plasticity (Robinson and Kolb, 1997, 1999). This is accompanied by an increase in spine density on the distal dendrites of these cells. These neuroadaptations in DA/accumbens systems specifically, then produce a pathological motivation for drugs, called compulsive "*wanting*."

Several points of this incentive sensitization theory are important in the current perspective. First, as a consequence of the dissociation between *liking* and *wanting*, the authors stress the fact that this theory does not simply account for the addiction by the positive and/or negative reinforcement value of the drugs, i.e., the addiction is not simply due to the desire to experience the positive hedonic effects of the drugs and/or to avoid aversive withdrawal symptoms, as proposed in other theories (e.g., Koob et al., 1989; Markou et al., 1993). The incentive salience theory explicitly shifts the hypothesis away from the conjonctural reinforcement aspect toward the structural alterations aspects. For example, Robinson and Berridge (2000, p. S96) state: "Perhaps the most remarkable feature of sensitization is its persistence. Once they have been sensitized, animals may remain hypersensitive to the psychomotor activating effects of drugs for months or years." In other words still, it is clear that the *wanting* circuit not only operates as a driving, and sometimes rewarding, system, but it is also sensitive to long lasting adaptations, i.e., to *historical imprint*. This, then, is coherent with the historical dimension of *jouissance* defined by "this mark, consisting of the drive presenting itself with a certain insistence, in its status of referring to something memorable because it was remembered" (Lacan, 1986/1959–1960, p. 209).

Further, the incentive sensitization theory also includes several aspects, which makes this theory a truly *psychological* theory. First, the theory of Robinson and Berridge (2000, p. S105) fully acknowledges the functional status of *representations* in this incentive salience process, e.g., "It is further hypothesized that the psychological process that leads to "*wanting*" involves the attribution of attractive salience to stimuli *and their representations*, a process we call incentive salience attribution. (...) We have suggested it is the process of incentive salience attribution that transforms the sensory features of ordinary stimuli or, more accurately, *the neural and psychological representations* of stimuli, so that they become especially salient stimuli, stimuli that "grab the attention," that become especially attractive and wanted, thus approach and guiding behavior to the goal." This role for representations is also logical in a action-centred rather than a stimulus-centred perspective, since it is known that preparation of an action as well as anticipation, imagination, remembering etc. of that action share a common motor imagery (Decety, 1996) and that this imagery could be the substrate of its representation (Jeannerod, 1994). Second, these representations can also be *unconscious*. For example, in addicts, doses of drugs that are too low to produce any conscious experience of pleasure can activate implicit *wanting* as indicated by an increase in drug-seeking behavior. Robinson and Berridge (2000, p. S104) propose: "the incentive-sensitization theory holds that drugs can activate positive core processes of motivation in the absence of conscious awareness, so that positive effects may not be indicated on any scale of subjective affective intensity. Indeed, the neural system responsible for incentive salience attribution can sometimes produce *wanting*, in the absence of conscious awareness of *wanting* itself (Robinson and Berridge, 2000, p. S105; see also Berridge, 1996, 1999). For example, the brief subliminal (i.e., unconscious) presentation of faces expressing positive emotions can activate implicit *wanting* increasing subsequent consumption of a beverage (Berridge and Winkielman, 2003). Robinson and Berridge (2000, p. S106) add: "Activation of this system (...) can act sometimes as an unconscious motivational process." In other words, the incentive salience theory can account for *an unconscious representation unconsciously inducing an intentional body investment or motor tension* – which is, in our opinion, also a highly psychoanalytic idea. The sensitized pathways, the neuroadaptations in the *wanting* system, are not simply sitting there, but form an active past, which has the continuous potential to press for action., i.e., which "unsubdued, pushes ever forward."

In this incentive salience framework, the clinical link between *wanting* and *jouissance* is quite direct: when the *wanting* system is activated implicitly, it can instigate and guide behavior without a person necessarily having conscious emotion, desire, or a declarative goal (Robinson and Berridge, 2003, p. 36). This kind of perplexity pertains clinically to a whole variety of behaviors which people persist in having, even if they are neither pleasurable, reasonable nor desirable, and even if they are negative or destructive. This is keenly observed in clinics: addicts maintain their consumption while they "may report they are miserable, their life is in ruins, and that even the drug is not that great anymore. They are themselves bewildered by the intensity of their own compulsive behavior[17]" (Robinson and Berridge, 2000, p. S106). Often the addict describes his behavior as simply an overwhelmingly strong craving that cannot be denied. Strikingly, these are the very type of clinical observations which have originally led to the necessity of thinking the concept of *jouissance* in psychoanalysis. Moreover, addiction has often been the terrain *par excellence* for the psychoanalytic description of *jouissance* (Braunstein, 1992;

[17] And the authors add this very psychoanalytic observation: "Indeed, addicts probably have no more insight into what motivates their daily behavior than do the rest of us; which is arguably, not much."

Delourmel, 2009), with as a basic tenet that it is not the pleasure of the consumption but the *jouissance*, which ties the subject to his addiction. Robinson and Berridge (2000, p. S105) understand reward starting as the combination of *liking* and *wanting* but stress that unlike the wanting systems, the neural systems that mediates the subjective pleasurable effects of drugs do not appear to sensitize. They add: "This may be why addiction is characterized by an increasing dissociation between the incentive value of drugs (how much they are wanted) and their subjective pleasurable effects (how much they are liked). With the development of an addiction drugs become pathologically wanted ("craved") and this can occur even if drugs are liked less and less." Again, the parallel with a psychoanalytic reading is striking: the reward as the combination of *liking* and *wanting* could correspond to the inaugural moment of *jouissance*, marking the adequate act which also brings pleasure. The dissociation between pleasure and enjoyment, moreover, could resonate with so-called *morbid jouissance* which accounts for the persistence of behaviors, which may[18] once have been adequate. However, even if they are no longer pleasurable, since they were effectively registered in memory, they will not fade away but will persist and push for their repetition, while most often remaining beyond conscious understanding (see also Johnson, 2008). Indeed, as said (see Commemoration of a Trait, Complying to Repeat), *jouissance* can persist independently of the object and action still being adequate in respect to the body need or drive from which they historically originated.

## CONCLUSION

In other words, it seems that the parallels between the different dimensions of the psychoanalytic concept of *jouissance* and the different aspects of the NAS-DA physiology are quite striking. At the level of the body, the NAS-DA has been proposed to function as a basic *drive* system much in the same way as described by Freud; *jouissance* then arises when this system goes awry, namely when the action is invested in and for itself, which is structurally bound to happen, as is shown in the phenomena of e.g., autoshaping. The NAS-DA is also the body system which tags actions which have brought (unexpected) reward and as a result of this tagging, a new encounter with the incentive stimulus will fuel a reserve of body energy motivating the organism to search the reward (or to avoid the aversive situation). This highly resonates with Freud's experience of satisfaction where either a bodily need, or a new encounter with "the Thing," will reactivate the mnemic motor image for action upon this "Thing." The tension induced by this reactivation, again, we have referred to as *jouissance*. Third, the mesolimbic NAS-DA is also the axis which functions in a constant instable balancing between reward and anxiety, reflecting the flimsy boundary between enjoyment and pain described for *jouissance*. At the level of the (organism's) history, the NAS-DA is the central operator in the so-called incentive salience theory, which describes how neuroadaptations due to reward can sensitize selectively the *wanting* system while leaving the hedonics or *liking* unchanged. This theory could therefore account for Lacan's historical dimension of *jouissance* defined as a mark referring to something memorable and commemorating an irruption of enjoyment. In both theories the memory traces relentlessly push for action, i.e., push for their repetition, which can explain the perplexifying persistence of behavior while it is no longer pleasurable, and even when it becomes damaging, such as in addiction. For all these reasons, *jouissance* could be described as an accumulation of body tension, fuelling for action, but continuously balancing between reward and anxiety, and both marking the physiology of the body with the history of its commemoration and arising from this inscription as a constant push to act and to repeat. Moroever, it seems that the mesolimbic NAS-DA is a reasonable candidate for its underlying physiological architecture.

[18] *Or may not*: Indeed, in *Beyond the pleasure principle* Freud (1955/1920) explains how a subject may also comply to repeat actions which were never pleasurable or adequate in the first place. He further indicates that the binding effect, which is a first necessary step toward discharge, is in this repetition probably the decisive element. In other words, acting upon a traumatic experience, even if this action is inadequate in bringing relief, is, in and by itself better than sideration, because the mere action channels the threatening accumulation of quantities toward a dischargeable motor form.

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# Neural activity in relation to empirically derived personality syndromes in depression using a psychodynamic fMRI paradigm

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**Objective:** The heterogeneity between patients with depression cannot be captured adequately with existing descriptive systems of diagnosis and neurobiological models of depression. Furthermore, considering the highly individual nature of depression, the application of general stimuli in past research efforts may not capture the essence of the disorder. This study aims to identify subtypes of depression by using empirically derived personality syndromes, and to explore neural correlates of the derived personality syndromes.

**Materials and Methods:** In the present exploratory study, an individually tailored and psychodynamically based functional magnetic resonance imaging paradigm using dysfunctional relationship patterns was presented to 20 chronically depressed patients. Results from the Shedler–Westen Assessment Procedure (SWAP-200) were analyzed by Q-factor analysis to identify clinically relevant subgroups of depression and related brain activation.

**Results:** The principle component analysis of SWAP-200 items from all 20 patients lead to a two-factor solution: "Depressive Personality" and "Emotional-Hostile-Externalizing Personality." Both factors were used in a whole-brain correlational analysis but only the second factor yielded significant positive correlations in four regions: a large cluster in the right orbitofrontal cortex (OFC), the left ventral striatum, a small cluster in the left temporal pole, and another small cluster in the right middle frontal gyrus.

**Discussion:** The degree to which patients with depression score high on the factor "Emotional-Hostile-Externalizing Personality" correlated with relatively higher activity in three key areas involved in emotion processing, evaluation of reward/punishment, negative cognitions, depressive pathology, and social knowledge (OFC, ventral striatum, temporal pole). Results may contribute to an alternative description of neural correlates of depression showing differential brain activation dependent on the extent of specific personality syndromes in depression.

**Keywords: depression, psychodynamic diagnosis, fMRI, Shedler–Westen Assessment Procedure, personality syndrome**

## INTRODUCTION

According to the WHO depression is one of the most prevalent diseases worldwide (World Health Organization, 2002) that goes along with substantial symptom severity and role impairment (Kessler et al., 2003) and is therefore a major public health issue. The distinction between different forms of chronic depression in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) has recently been criticized because patients with dysthymia, double depression, or major depressive disorders seem to have only minor differences in their clinical features, family history, and treatment response (McCullough et al., 2000, 2003; Klein et al., 2004). On the other hand, there is obvious heterogeneity between patients with depression, which is clinically relevant but cannot be captured adequately with existing descriptive systems of diagnosis (DSM-IV, APA, 1994; ICD-10, WHO, 1992). As for the idea of "clinical relevance," subtyping depression is not only important for the sake of taxonomic clarity. Dwelling into the complexities of depression by garnering a more nuanced picture of the disorder might also facilitate case conceptualization and treatment planning for clinicians. Relevant in the context of our study, a differentiated picture of depression and its neurobiological underpinnings examined by brain imaging might eventually lead to different therapeutic approaches or be useful as a predictor for relapses.

Among other important approaches to define depression and its subtypes, Bleichmar (2010) describes different pathways of

pathological mourning which is related to chronic depression and factors of maintaining depression. He suggests that the essential component of pathological mourning is the feelings of helplessness and hopelessness related to the loss of a significant other or a feature of a significant other (e.g., love). Bleichmar (2010) distinguishes at least two subtypes in pathological mourning: while the first subtype is related to a past loss, patients of the second subtype are suffering from a current loss of internal or external causes (e.g., loss of employment). Especially the second subtype is characterized by relationship anxiety and hostility toward others which often isolates them from corrective or helpful relationship experiences. Aggressiveness and ambivalence toward others as a certain subtype of depression has also been described by Freud (1917) in "Mourning and Melancholia" and was confirmed in psychoanalytic clinical work by Klein (1940) and Jacobson (1971). According to Bleichmar (2010), understanding the complex interaction of etiology and maintaining factors of depression is important to establish individually tailored treatment modalities. In Bleichmar's view, subtypes of depression are best understood within a dimensional model of the psyche, which resembles the psychoanalytic approach to nosology in contrast to approaches using isolated categories, such as the DSM. Regarding another alternative approach to differentiate within the spectrum of patients with depression that stands in contrast to the DSM-IV typology of depression, Blatt and Luyten (2009) have suggested to distinguish between introjective and anaclitic depression (for a more basic criticism on the DSM-IV and depression compare Luyten et al., 2006). The anaclitic depression is based on feelings of loneliness, neglect, abandonment, and staying in relationships whereas the introjective depression is centered on self-worth, failure, guilt, and a withdrawal from relationships. The introjective pole has been related to chronic depression and poorer treatment outcome (Blatt et al., 2001; Blatt, 2004, 2008). Tackling the issue of heterogeneity in depression and using a diagnostic method closer to clinical inference, Westen and Shedler (1999b) and Shedler and Westen (2004) derived five empirical subtypes of depression relating to different triggers for depressive moods: (a) avoidant, (b) high-functioning, (c) dysregulated, (d) dependent, and (e) hostile-externalizing.

In general, complex clinical inferences are based on a variety of psychological data including not only what a patient says but how something is said as well as how this affects the clinician emotionally (Westen and Arkowitz-Westen, 1998). This way of thinking and inferring is the core of psychodynamic understanding (Kernberg, 1975; McWilliams, 1994) which is in contrast to rather technical diagnoses that list symptoms without relating them to each other. In a psychodynamic approach, clinicians do not count symptoms but compare an individual patient with a prototype of the disorder (Blashfield et al., 1985; Kim and Ahn, 2002). However, clinical diagnoses are found not to be reliable and are therefore considered not being useful in empirical research. The Shedler–Westen Assessment Procedure (SWAP-200; Shedler and Westen, 2007; Westen et al., 2011) tries to bridge the gap between clinical practice and empirical research by providing a diagnostic tool that relies on clinical judgment with a standardized vocabulary and Q-sort method to obtain meaningful data on personality pathology independent from theoretical approach. Hence, the SWAP-200 is a theoretically and empirically well-grounded method to encounter the phenomenological heterogeneity we face on the clinical side of depression.

The clinical heterogeneity in depression is comparably evident from the neurobiological perspective. Over the last 15 years, many studies with increasing sophistication and reviews could narrow down the brain areas presumably involved in the pathophysiology of depression [amygdala, basal ganglia, prefrontal cortex, anterior cingulate cortex (ACC), etc.] but there is still no consensus regarding for instance the hemisphere in which these changes are most prominent or the exact direction of the differences in activation (Drevets, 2000; Davidson et al., 2002; Mayberg, 2003; Fitzgerald et al., 2006; Steele et al., 2007). A comprehensive meta-analysis found only limited overlap between studies exploring brain changes in depression: prefrontal cortex, ACC, insula, and superior temporal gyrus were found to be relatively hypoactive, whereas several limbic, subcortical, and frontal regions showed hyperactivity (Fitzgerald et al., 2008). Besides the above mentioned structures, a recent meta-analysis stresses the importance of an increased pulvinar nucleus baseline activity in patients with depression, which increases the responsiveness of the salience network and hinders the prefrontal structures from reappraisal (Hamilton et al., 2012). However, considering those data the heterogeneity of the neural correlates of depression prevails. There are various methodological reasons for the problems we encounter with neuroimaging data (Gusnard et al., 2001; Logothetis, 2008; Kriegeskorte et al., 2009; Vul et al., 2009). In addition to the heterogeneity of patient samples that also plagues neurobiological studies, one central problem could be the mere application of generalized stimuli in the vast majority of neuroscientific studies in the field. Considering the highly individual nature of depression in terms of history, relationship patterns, personality functioning, and others, merely applying experiments with general stimuli (e.g., emotional faces, Ekman and Friesen, 1976; or pictures from the International Affective Picture System, Lang et al., 1997) hardly captures the essence of the disorder. Consequently, the individualization of experimental paradigms could tackle the issue of heterogeneity in depression as well as in its neurobiological underpinnings. It is only through a differentiated and individualized approach that we could adequately assess the phenomenon of depression in its nuances. Amongst other authors, this has been clearly stated by Kessler et al. (2011b) for the case of the neurobiology of depression and recently for the investigation of neural correlates of changes after psychodynamic psychotherapy (Böker et al., 2013). For the clinical side, concepts like the SWAP-200 contribute to a more nuanced and differentiated view of each patient's depression. In an endeavor to account for both aspects described above, our study presented here uses a laborious but rich description of depression subtypes by deriving dimensional personality syndromes with the SWAP-200 in combination with a complex experimental functional magnetic resonance imaging (fMRI) paradigm applying individualized stimuli. In our opinion, individualization is the pivotal aspect when investigation the neurobiology of depression. We hence developed our own set of stimuli consisting of sentences describing each patient's dysfunctional relationship pattern and psychodynamic conflict-related

themes (Kessler et al., 2011a). The sentences were derived from a clinical interview based on operationalized psychodynamic diagnosis (OPD; OPD-Task-Force, 2008) and were suitable for presentation in the fMRI scanner (see Materials and Methods for details).

Patients were confronted with their individualized psychodynamic relation themes in the fMRI scanner to increase the impact and specificity of brain responses. Part of the data of this experiment was already presented (Kessler et al., 2011a). This report adds a rich clinical aspect: in addition, two interviews with patients were used for the assessment of the SWAP-200 to obtain data on personality functioning in terms of a dimensional approach which is in line with the research suggestions from DSM-V (Skodol et al., 2011). Based on this assessment a Q-factor analysis extracted two factors describing meaningful clinical personality phenomenology. Patients' scores on the spectrum of those extracted factors were then correlated with relative brain responses to the OPD stimuli. Since the exact amount and nature of the SWAP-200 factors were unknown before data collection, we did not follow any specific hypotheses. The main study question was hence on a more exploratory level if personality syndromes in depression correlate with brain activity during a depression-related and individualized experiment.

## MATERIALS AND METHODS

### PARTICIPANTS

Participants comprised 20 unmedicated patients [age *M* (SD) = 39.2 years (12.7), range 20–64 years, 16 women] with recurrent major depressive disorder. All patients were in a major depressive episode during recruitment. Data of 18 of those patients have been included in a previous report comparing patients with controls (Kessler et al., 2011a). Patients were recruited from a psychoanalytic institute and diagnosed by two trained clinicians using the structured clinical interviews I and II for DSM-IV (SCID; German version; Wittchen et al., 1996). They reported between 1 and 10 depressive episodes [*M* (SD) = 4.00 (3.58)], and their age at first occurrence of depression was between 8 and 40 years [*M* (SD) = 20.00 (9.52)]. Some patients had received various types of medication and psychotherapies during the course of their disease but had not received treatment within at least 6 months prior to inclusion in the study. After study inclusion and baseline assessments all patients started a psychoanalytic psychotherapy. Exclusion criteria were other psychiatric conditions, substance abuse, significant medical or neurological conditions, or eye problems. The study protocol was approved by the ethics committee of the University of Ulm.

### CLINICAL MEASURE

The SWAP-200 is a Q-Sort procedure with 200 clinical statements that have to be sorted in a fixed distribution (Westen and Shedler, 1999a,b). Items were drawn from the clinical literature of the past 50 years, research literature on coping, defense and affect regulation, interpersonal pathology, and personality research in non-clinical populations. Each item may describe a patient well, a little or not at all. Coders sort all items into a fixed distribution, ranking from most descriptive (value 7) to least descriptive (value 0). The SWAP-200 is based on a Q-Sort-method which forces the coder to rank the 200 items in a fixed distribution. The instrument is available online (www.SWAPassessment.org).

Items are constructed jargon-free and if possible close to observation, e.g., "tends to abuse alcohol," "tends to have numerous sexual involvements; is promiscuous." Statements that describe psychic processes, that have to be inferred from the interview situation or descriptions from the patients, are constructed in clear unambiguous language, e.g., "tends to be conflicted about authority (e.g., may feel s/he must submit, rebel against, win over, defeat, etc.)" or "appears to have little need for human company or contact; is genuinely indifferent to the presence of others."

The SWAP-200 shows high inter-rater reliability between $r = 0.80$ and 0.90 (Shedler and Westen, 1998; Westen and Muderrisoglu, 2003; Marin-Avellan et al., 2005; Westen and Shedler, 2007). It has been validated on 797 US-American psychotherapists of different therapeutic approaches of whom 72.7% concluded that the SWAP-200 allows them to describe the most important aspects of their patients (Westen and Shedler, 1999a); convergent and discriminant validity was also confirmed (Westen and Shedler, 1999a,b; Cogan and Porcerelli, 2005).

Although it is recommended to score the SWAP-200 using the Clinical Diagnostic Interview (Westen, 2002), it is also possible to use it with other diagnostic interviews or on the basis of at least five therapeutic sessions (Westen and Weinberger, 2004). In the present study, the SWAP-200 was scored by two clinical psychologists in a consensus rating on the basis of two video- and audiotaped clinical interviews with each participant: the Scales of Psychological Capacities Interview (SPC; Huber et al., 2006a,b) and an interview based on the OPD (OPD-Task-Force, 2008).

### FACTOR ANALYSIS

We applied Q-factor analysis to identify personality syndromes empirically. Q-factor analysis enables groupings of patients with personality features similar to one another and distinct from those of patients in other groupings. The statistical procedure is identical with conventional factor analysis but is applied to cases rather than variables. Therefore, our data matrix was transposed, using cases as variables (columns) and SWAP-200 items as cases (lines) (cp. Block, 1978; Westen et al., 2011). This leads to 200 "cases" with 20 variables each which is sufficient to conduct a principle component analysis. Classical factor analysis identifies groups of similar variables that belong to a common underlying factor. In contrast, Q-factor analysis identifies groups of similar people who share characteristics, in this case common personality syndromes. The findings reported here are based on a principle component analysis without rotation. We decided against rotation in terms of a "simple structure approach" due to theoretical reasons because we expected to find a common personality factor as well as factors that differentiate between patients (Russell, 2002). Using a varimax rotation, for example, would force a solution with two or more orthogonal factors. Since all patients were diagnosed with depression, we expected that all participants would load on one factor related to depression but differ in their factor loadings on other factors. Therefore, using a principle component analysis without rotation would allow analyzing factors that are closer to the clinical phenomenon of depression. Statistical analysis was performed using the Statistical Package for the Social Science (SPSS) version

19.0. After identifying factors with principle component analysis, we analyzed those 20 items from the SWAP-200 loading highest on each factor. Descriptive core features of each factor dimension were summarized and interpreted by two clinicians (Henrik Kessler and Svenja Taubner) to obtain a diagnostic description of each factor.

### STIMULI, PROCEDURE, AND EXPERIMENT

Individualized stimuli were generated based on an interview according to the system of OPD (OPD-Task-Force, 2008) conducted by a trained clinician (Henrik Kessler). Videotaped material was rated independently by two to three expert raters (OPD-trainers). Typical dysfunctional interpersonal relations were identified and served as basis for the experimental stimuli ("OPD sentences"). Sentences described an individual problematic interpersonal relation typical of their depressive cognitions. Four individually tailored sentences were selected for each participant representing the typical dysfunctional relationship theme of each person (e.g., "You wish to be accepted by others.", "Therefore you do a lot for them.", "That is often too close for them, so they retreat.", "Then you feel empty and lonesome."). These individual sentences served as stimuli during the fMRI session (experimental or OPD condition). The control condition ("traffic") comprised four sentences, which described a stressful traffic situation ("The other driver makes a mistake.", "You are very upset about this.", "You react to the other driver.", "But he reacts inadequately."). Prior to testing, participants were asked to remember a recent and stressful situation they had experienced in traffic. The rationale behind this control condition was to induce negative emotions and recall autobiographical memories including human interactions, but without engaging in specific depression-related material. In order to separate the two conditions (OPD and traffic), and let subjects calm down after emotionally demanding sentences, "relaxation" sentences were inserted between conditions. Those sentences instructed participants to relax. Whereas the OPD sentences were derived individually for each person, "relaxation" and "traffic" were the same across all subjects. OPD sentences were slightly but significantly longer [$M$ (SD) = 50.8 (8.0) characters] than "traffic" sentences (44 characters, $p < 0.001$).

Four to six weeks prior to the fMRI assessment, participants filled out informed consent forms and were interviewed (SCID I+II, OPD, SPC). At the beginning of the fMRI session, they were briefed, saw their individual OPD sentences prior to actual scanning and were asked, whether the sentences fit and enticed them to think about their problematic relations. After completion of assessments, all patients started psychodynamic treatment.

### IMAGE ACQUISITION AND ANALYSIS

Sentences were presented by a projector onto a screen watched by the participants via a mirror while lying in the scanner. The four sentences of a condition (OPD, traffic, relaxation) were presented for 7.5 s each, resulting in 30 s blocks. During the OPD block participants were asked to mentally engage in situations with significant others, as described by the OPD sentences. They received no instruction to regulate their emotions, but were asked to let spontaneous thoughts, emotions, and memories come to mind. "Traffic" and "relaxation" conditions also comprised four sentences with each lasting 7.5 s. The instructions were to mentally engage either in the traffic situation or to relax. In total, 12 "relaxation," 6 "traffic," and 6 "OPD" blocks were presented (white Arial font, size 16, black background). Blocks were separated by a 5-s fixation cross. The entire experiment lasted approximately 15 min.

Data were obtained using a 3 T SIEMENS Magnetom Allegra head scanner (Siemens, Erlangen, Germany). Participants were positioned on the scanner couch and wore foam earplugs to reduce scanner noise. An experienced psychotherapist not involved in the therapy of the patients (Svenja Taubner or Henrik Kessler) assisted with the setup procedure and coached the participants throughout the experiment. Data acquisition started with anatomical images (3D high resolution T1-weighted isotropic volume, MPRAGE-sequence [MPRAGE = Magnetization Prepared Rapid Gradient Echo (18)]; repetition time (TR) = 2.3 s, field of view (FOV) = 256 mm × 256 mm × 176 mm, echo time (TE) = 4.38 ms, inversion time (TI) = 900 ms, flip angle = 8°, 1 mm isovoxel, total acquisition time 14.45 min). Functional scans were performed using a single shot echo planar imaging (EPI) sequence. A total of 365 T2*-weighted whole-brain volumes were acquired (EPI-sequence; TR = 2500 ms, TE = 30 ms, flip angle = 90°, FOV = 192 mm, matrix 64 × 64, 44 slices, slice thickness 3 mm, interleaved acquisition order, AC–PC (anterior commissure–posterior commissure) orientation, total acquisition time: 15.18 min).

Data were analyzed and visualized using Brain Voyager QX 1.10 to 2.2 (Brain Innovation, Maastricht, Netherlands). Preprocessing: functional data were slice-time corrected and motion was corrected relative to the first volume of the run. To remove low frequency drifts, data were high-pass filtered (three cycles, three sine waves fall within the extent of the data). Structural and functional data were transformed into the standard space of Talairach and Tournoux, data points were labeled using Talairach Daemon. The design matrix was modeled using the two gamma hemodynamic response function. Functional data were smoothed using an 8-mm full width at half maximum (FWHM) isotropic Gaussian kernel. A random effects analysis based on $z$-transformed functional data was conducted including the within-factor CONDITION (OPD vs. traffic sentences). Motion-correction parameters were included in the generalized linear model (GLM) as regressors of no interest.

Whole-brain correlational analyses were conducted based on individual values within the SWAP-200 factors extracted by Q-factor analysis and beta values for the contrast OPD > traffic for all subjects. Whole-brain statistics were conducted and maps are shown with a threshold of $p < 0.001$, uncorrected. A cluster size threshold of 16 voxels was consistently applied. All active voxels are displayed in native resolution without interpolation and plotted on the Talairach-transformed brain; Talairach coordinates are reported as TAL $x$, $y$, $z$.

## RESULTS

### SWAP-200 FACTOR ANALYSIS

The principle component analysis of SWAP-200 items from all 20 patients lead to a two-factor solution (eigenvalues: 9.30, 1.55) accounting for 54.23% of the variance, Factor 2 explained 7.8% and Factor 1 explained 46.5% of the variance.

The 20 items with the highest factor loadings on Factor 1 could be summarized as the following: one set of items described depressive symptoms (Items 1, 3, 4, 5, 6, 10, and 11, compare **Table 1**), another set of items resembled relationship problems and relationship anxieties typical for depressed patients, e.g., the inhibition or questioning of own wishes and problems in expressing anger (items 2, 7, 9, 12, 14, 15, 16, 17, 18). Two items could be interpreted as adding a momentum of self-criticism to the factor (8, 13). Because self-criticism was only represented by two items and the main focus was on general depressive symptoms and typical relationship problems the factor was named "*Depressive Personality.*" With those general characteristics of items being part of depression itself, all patients scored high on this factor with no meaningful variation (cp. **Table 3**).

In contrast, the 20 highest SWAP-200 items loading on Factor 2 (compare **Table 2**) seemed to be more specific for specific personality syndromes in depression and hence displayed greater variation and could better differentiate between subjects. Items of this factor broadly reflected characteristics that could be described as highly emotional, externally oriented (externalizing), and hostile. In various items emotions of high intensity (e.g., 1, 7) were evident in different contexts. Furthermore, many items described intense emotional interactions with others, pointing to an orientation toward the external world (as opposed to a social withdrawal evident in other types of depression). Those interactions could reflect dependency (e.g., 9, 15, 19) but mainly had a hostile or aggressive tone (e.g., 2, 5, 18, 20). In conjunction, subjects scoring high on this factor seemed to engage widely in interactions with others, typically in a hostile or dependent way with intensive emotions involved. This factor was therefore named after the dominant features "*Emotional-Hostile-Externalizing Personality*" resembling two subtypes of depression that have been described before (Shedler and Westen, 2004).

Factors 1 and 2 were uncorrelated ($r = -0.27$, $p = 0.26$)[1].

## NEUROIMAGING RESULTS

The whole-brain correlational analysis yielded no significant correlation for Factor 1. Concerning Factor 2, four regions with significant positive correlations ($p < 0.001$, cluster size threshold of 16 voxels) between patients' factor scores on the SWAP-200 factor "Emotional-Hostile-Externalizing Personality" and beta values for the contrast OPD > traffic could be identified: a large cluster in the right orbitofrontal cortex [OFC; anatomically within the inferior frontal gyrus (IFG)], the left ventral striatum (caudate head), a small cluster in the left temporal pole and another small cluster in the right middle frontal gyrus (functionally within the prefrontal cortex). See **Table 4** and **Figure 1** for details.

[1]We tested another principle component analysis using varimax rotation to compare results. This also led to a two-factor solution but patients' factor scores were highly correlated in this sample ($r = 0.89$) which confirmed our theoretical assumption to avoid a simple structure approach with this material.

**Table 1 | The 20 highest factor loadings on SWAP-200 items for Q-Factor 1 ("Depressive Personality").**

| | 20 highest factor loadings with SWAP-200 items on Factor 1 | Factor loadings (*z*-values) |
|---|---|---|
| 1 | Tends to feel unhappy, depressed, or despondent | 3.089 |
| 2 | Tends to fear s/he will be rejected or abandoned by those who are emotionally significant | 2.855 |
| 3 | Tends to feel listless, fatigued, or lacking in energy | 2.850 |
| 4 | Tends to blame self or feel responsible for bad things that happen | 2.774 |
| 5 | Appears to find little or no pleasure, satisfaction, or enjoyment in life's activities | 2.417 |
| 6 | Tends to feel s/he is inadequate, inferior, or a failure | 2.245 |
| 7 | Has difficulty acknowledging or expressing anger | 2.034 |
| 8 | Tends to be self-critical; sets unrealistically high standards for self and is intolerant of own human defects | 2.012 |
| 9 | Is simultaneously needy of, and rejecting toward, others (e.g., craves intimacy and caring, but tends to reject it when offered) | 2.006 |
| 10 | Tends to feel empty or bored | 2.001 |
| 11 | Tends to feel guilty | 1.900 |
| 12 | Tends to avoid confiding in others for fear of betrayal; expects things s/he says or does will be used against him/her | 1.848 |
| 13 | Tends to be insufficiently concerned with meeting own needs; appears not to feel entitled to get or ask for things s/he deserves | 1.763 |
| 14 | Tends to express aggression in passive and indirect ways (e.g., may make mistakes, procrastinate, forget, become sulky, etc.) | 1.703 |
| 15 | Tends to feel misunderstood, mistreated, or victimized | 1.687 |
| 16 | Tends to be overly needy or dependent; requires excessive reassurance or approval | 1.683 |
| 17 | Tends to feel s/he is not his/her true self with others; tends to feel false or fraudulent | 1.661 |
| 18 | Tends to be inhibited or constricted; has difficulty allowing self to acknowledge or express wishes and impulses | 1.635 |
| 19 | Tends to be critical of others | 1.625 |
| 20 | Tends to be anxious | 1.625 |

**Table 2 | The 20 highest factor loadings on SWAP-200 items for Q-Factor 2 ("Emotional-Hostile-Externalizing").**

| | 20 highest factor loadings with SWAP-200 Items on Factor 2 | Factor loadings (*z*-values) |
|---|---|---|
| 1 | Tends to react to criticism with feelings of rage or humiliation | 3.134 |
| 2 | Tends to feel misunderstood, mistreated, or victimized | 2.806 |
| 3 | Tends to be emotionally intrusive; tends not to respect others' needs for autonomy, privacy, etc. | 2.487 |
| 4 | Tends to think others are envious of him/her | 2.436 |
| 5 | Is quick to assume that others wish to harm or take advantage of him/her; tends to perceive malevolent intentions in others' words and actions | 2.397 |
| 6 | Tends to blame others for own failures or shortcomings; tends to believe his/her problems are caused by external factors | 2.262 |
| 7 | Emotions tend to spiral out of control, leading to extremes of anxiety, sadness, rage, excitement, etc. | 2.131 |
| 8 | Tends to be competitive with others (whether consciously or unconsciously) | 2.009 |
| 9 | Tends to be overly needy or dependent; requires excessive reassurance or approval | 1.670 |
| 10 | Is preoccupied with the feeling that someone or something has been irretrievably lost (e.g., love, youth, the chance for happiness, etc.) | 1.605 |
| 11 | Tends to feel like an outcast or outsider; feels as if s/he does not truly belong | 1.574 |
| 12 | Tends to feel helpless, powerless, or at the mercy of forces outside his/her control | 1.521 |
| 13 | Tends to get into power struggles | 1.479 |
| 14 | Tends to hold grudges; may dwell on insults or slights for long periods | 1.471 |
| 15 | Tends to become attached quickly or intensely; develops feelings, expectations, etc. that are not warranted by the history or context of the relationship | 1.416 |
| 16 | Tends to feel envious | 1.405 |
| 17 | Has fantasies of unlimited success, power, beauty, talent, brilliance, etc. | 1.372 |
| 18 | Tends to be arrogant, haughty, or dismissive | 1.330 |
| 19 | Appears to fear being alone; may go to great lengths to avoid being alone | 1.213 |
| 20 | Tends to be angry or hostile (whether consciously or unconsciously) | 1.161 |

## DISCUSSION

In the growing area of neuropsychoanalysis (Solms and Turnbull, 2011), this exploratory study can be described as "psychoanalytically informed neuroscience" that unifies an experimental design with a rich clinical assessment of patients with chronic depression to associate with brain activity. The present study brought together two issues regarding the heterogeneity in depression and analyzed brain data in an exploratory way. We used the SWAP-200 Q-Sort procedure to provide a clinically meaningful characterization of a sample of 20 chronically depressed patients and describe its correlations with brain activation using an individually tailored and depression-related paradigm. Twenty patients with chronic depression were confronted with their individual dysfunctional relationship pattern (derived from OPD) inside the fMRI scanner.

Entering the SWAP-200 items into a Q-factor analysis yielded two meaningful factors, "Depressive Personality" and "Emotional-Hostile-Externalizing Personality." Only the second factor was differentiating between patients (high and low factor scores). Patients were distributed along this factor reflected by differences in emotion accompanied by relationship difficulties and hostile attributions toward others. In an exploratory analysis, values for both factors were correlated with beta values from the brain activity when patients were confronted with their dysfunctional relationship pattern (relative to a control condition). Interestingly, this whole-brain analysis yielded no correlations with the factor "Depressive Personality" and four distinct areas with Factor 2, whose activity significantly correlates with the extent to which patients are "Emotional-Hostile-Externalizing": a large cluster in the right OFC (anatomically within the IFG), the left ventral striatum (caudate head), a small cluster in the left temporal pole, and another small cluster in the right middle frontal gyrus (functionally within the prefrontal cortex). Since this was an exploratory study with an open approach to analyses (Q-factor analysis and brain–behavior correlations) and no specific hypotheses, the discussion of the possible meaning and implication of our results is of course speculative in nature. Additionally, our results were correlational. Hence causal inferences could not be made and patients are distributed along a spectrum comprising the factor "Emotional-Hostile-Externalizing Personality" rather than forming a distinct subgroup. The fact, that – despite an open whole-brain approach – there were only four areas evident, of which three fit functionally into the framework of "Emotional-Hostile-Externalizing" (see below) encourages us to consider this study as hypothesis-generating. Future studies could chose subjects based on their characteristics in terms of "Emotional-Hostile-Externalizing Personality" (e.g., high vs. low) and conduct the fMRI experiment

**Table 3 | Factor scores of 20 patients on the factor "Depressive Personality" and "Emotional-Hostile-Externalizing Personality."**

| | Factors | |
|---|---|---|
| | **Depressive Personality** | **Emotional-Hostile-Externalizing** |
| Patient 1 | 0.554 | 0.454 |
| Patient 2 | 0.765 | 0.170 |
| Patient 3 | 0.625 | −0.213 |
| Patient 4 | 0.782 | −0.045 |
| Patient 5 | 0.649 | −0.488 |
| Patient 6 | 0.791 | −0.078 |
| Patient 7 | 0.686 | −0.060 |
| Patient 8 | 0.628 | −0.412 |
| Patient 9 | 0.643 | 0.059 |
| Patient 10 | 0.843 | 0.034 |
| Patient 11 | 0.666 | 0.276 |
| Patient 12 | 0.650 | 0.061 |
| Patient 13 | 0.697 | −0.296 |
| Patient 14 | 0.649 | −0.116 |
| Patient 15 | 0.555 | 0.331 |
| Patient 16 | 0.605 | 0.463 |
| Patient 17 | 0.629 | 0.450 |
| Patient 18 | 0.702 | 0.000 |
| Patient 19 | 0.670 | −0.368 |
| Patient 20 | 0.762 | −0.059 |

with *a priori* hypotheses to reject or confirm if the brain areas found here actually are involved differentially when processing a dysfunctional relationship pattern.

As for the regions, OFC, ventral striatum, and temporal pole are all part of the limbic system, broadly involved in emotion processing (Olson et al., 2007; Kopell and Greenberg, 2008). Generally speaking, activity in the limbic system in response to personally relevant emotional situations (OPD relationship pattern) that increases with clinically validated emotionality of the patient ("Emotional-Hostile-Externalizing") is very plausible. In detail, OFC and ventral striatum together form a central part of the limbic loop in a recent model of basal ganglia functionality (Kopell and Greenberg, 2008). This limbic loop – as well as the OFC itself – is, amongst other functions, involved in emotion processing, the assessment of stimuli according to reward and punishment and reward based decision-making (Rolls, 2000). Interestingly, existing models differentiate between more lateral and more medial areas of the OFC providing different functions. In an early review (Kringelbach and Rolls, 2004), the authors argue for a relative specialization of the medial OFC in the processing of rewarding and the lateral OFC in the processing of punishing stimuli. The relative OFC activity in the current study is widespread but relatively more lateral and one characteristic of patients scoring high on the factor is their hostility toward others (with aspects like criticism, victimization, or grudge). Hence, the "punishing" aspect of dysfunctional relationship patterns presented in the fMRI could be relatively more important for patients with high hostile attributions. This "punishing" aspect is supposedly associated with a relatively lateral OFC activity.

On a more general level, the OFC is involved in emotional experiences and social behavior (Rolls et al., 1994; Hornak et al., 1996; Zald and Kim, 1996). This is interesting, since patients scoring high in the "Emotional-Hostile-Externalizing" factor display relatively greater involvement in social interactions (irrespective of valence) and have relatively more activity in the OFC.

Kircher et al. (2013) found the IFG (anatomical overlap with our OFC site) directly related to changes in symptom severity in panic disorder after a cognitive-behavioral psychotherapy. Before psychotherapy the relative stronger activation in the IFG in the group of patients was also related to a stronger connectivity between the IFG and the limbic system (amygdala, anterior insula, ACC). The authors tentatively speculated that specific cognitive processes in the IFG in terms of negative cognitions may trigger emotional processes. In our sample of chronically depressed patients, the relative higher activation in the OFC (anatomically IFG) may be related to stronger negative cognitions in patients scoring high in terms of hostile attributions toward others when being confronted with dysfunctional relationship patterns.

In itself, the ventral striatum is an area that has been repeatedly discussed in the pathophysiology of depression in several reviews and meta-analyses (Fitzgerald et al., 2008; Hamilton et al., 2012) and might also be a viable target for deep brain stimulation in otherwise treatment-resistant depression (Kopell and Greenberg, 2008). Hence, correlation between a clinical variable describing an aspect of depression and activity in the ventral striatum is very plausible.

The relationship-related aspects of patients scoring high on the factor "Emotional-Hostile-Externalizing" may also be related to the relative activation in the left temporal pole. This small region is also part of the limbic system and has been considered to be strongly involved in social and emotional processing (Olson et al.,

**Table 4 | Regions with significant positive correlation ($p < 0.001$, cluster size threshold of 16 voxels) between individual values within the SWAP-200 factor "Emotional-Hostile-Externalizing" and beta values for the contrast OPD > traffic.**

| **Regions** | **Side** | **BA** | **Cluster size** | ***X*** | ***Y*** | ***Z*** | ***R*** |
|---|---|---|---|---|---|---|---|
| Ventral striatum (caudate head) | R | | 594 | 13 | 18 | −9 | 0.74 |
| Inferior frontal gyrus (orbitofrontal cortex) | L | 47,11 | 6507 | −29 | 33 | −12 | 0.84 |
| Middle frontal gyrus | L | 10 | 675 | −33 | 42 | 20 | 0.77 |
| Superior temporal gyrus (temporal pole) | L | 38 | 567 | −38 | 14 | −36 | 0.81 |

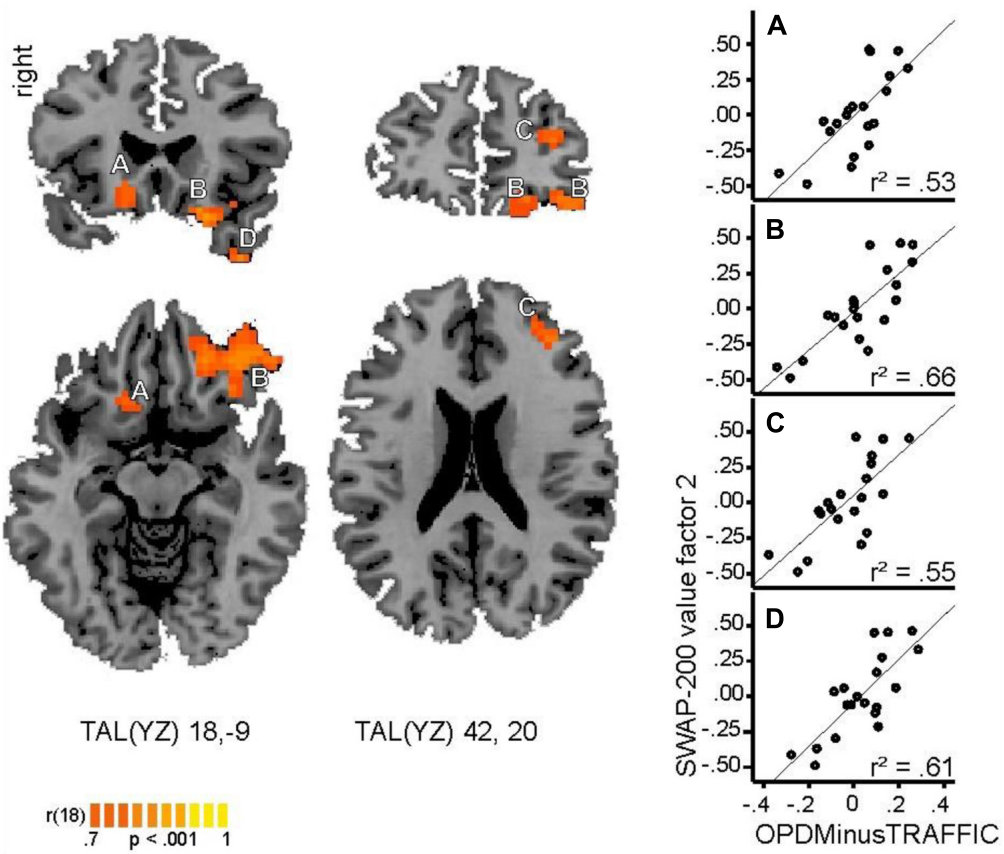


**FIGURE 1 | Regions with significant positive correlation ($p < 0.001$, cluster size threshold of 16 voxels) between individual values within the SWAP-200 factor "Emotional-Hostile-Externalizing" and beta values for the contrast OPD > traffic.** Cluster A: ventral striatum (caudate head), B: orbitofrontal cortex, C: prefrontal cortex, D: temporal pole. Coordinates are provided in Talairach space. Right side: correlation coefficients between beta values within each cluster and SWAP-200 values for Factor 2.

2007). Additionally, the temporal pole – especially on the left side – is discussed as being a core area for tasks involving "mentalizing" (Frith and Frith, 2003). The basic idea is that the temporal pole processes access to social knowledge and social scripts. Receiving input from all sensory modalities and the other parts of the limbic system, the temporal pole is active when recalling autobiographical information, putting recent stimuli in the context of past experiences in social interactions (Frith and Frith, 2003). This function could be linked with the aspect of stronger conflicted relationships within the SWAP-200 factor "Emotional-Hostile-Externalizing" when thinking about their individual repetitive interaction patterns.

In summary, we found in an open whole-brain correlation analysis that the degree of patients with depression to react with intense emotions, engage heavily in social interactions and tend to be or view their environment as hostile (SWAP-200 factor "Emotional-Hostile-Externalizing") correlated positively with relatively higher activity in three key areas involved in emotion processing, evaluation of reward/punishment, depressive pathology, negative cognitions, and social knowledge (OFC, ventral striatum, temporal pole). We speculate here, that those patients scoring higher in "Emotional-Hostile-Externalizing" reacted with stronger emotions when confronted with their dysfunctional relationship pattern, had a tendency to evaluate the stimuli as being more punishing or experienced stronger negative cognitions and engaged more intensively in the recall of social situations. Results may contribute to an alternative description of neural correlates of depression showing differential brain activation dependent on personality syndrome related subtypes of depression. Future studies should include other patient groups, e.g., anxiety disorders, to analyze whether the results reported here are specific to depression or have an overlap to other mental disorders.

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## AUTHOR CONTRIBUTIONS

Daniel Wiswede, Henrik Kessler, and Svenja Taubner have conducted the study. Daniel Wiswede was mainly responsible for fMRI-data acquisition and data analysis. Henrik Kessler and Svenja Taubner were responsible for participant recruitment, clinical assessments, and data analysis. Svenja Taubner assessed the SWAP-data and had the basic idea for this manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed in writing the manuscript.

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# Dream characteristics in a Brazilian sample: an online survey focusing on lucid dreaming

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During sleep, humans experience the offline images and sensations that we call dreams, which are typically emotional and lacking in rational judgment of their bizarreness. However, during lucid dreaming (LD), subjects know that they are dreaming, and may control oneiric content. Dreaming and LD features have been studied in North Americans, Europeans and Asians, but not among Brazilians, the largest population in Latin America. Here we investigated dreams and LD characteristics in a Brazilian sample ($n = 3{,}427$; median age = 25 years) through an online survey. The subjects reported recalling dreams at least once a week (76%), and that dreams typically depicted actions (93%), known people (92%), sounds/voices (78%), and colored images (76%). The oneiric content was associated with plans for the upcoming days (37%), memories of the previous day (13%), or unrelated to the dreamer (30%). Nightmares usually depicted anxiety/fear (65%), being stalked (48%), or other unpleasant sensations (47%). These data corroborate Freudian notion of day residue in dreams, and suggest that dreams and nightmares are simulations of life situations that are related to our psychobiological integrity. Regarding LD, we observed that 77% of the subjects experienced LD at least once in life (44% up to 10 episodes ever), and for 48% LD subjectively lasted less than 1 min. LD frequency correlated weakly with dream recall frequency ($r = 0.20$, $p < 0.01$), and LD control was rare (29%). LD occurrence was facilitated when subjects did not need to wake up early (38%), a situation that increases rapid eye movement sleep (REMS) duration, or when subjects were under stress (30%), which increases REMS transitions into waking. These results indicate that LD is relatively ubiquitous but rare, unstable, difficult to control, and facilitated by increases in REMS duration and transitions to wake state. Together with LD incidence in USA, Europe and Asia, our data from Latin America strengthen the notion that LD is a general phenomenon of the human species.

**Keywords: lucid dreaming, dreams, nightmares, REM sleep, dream features**

## INTRODUCTION

Dreams are characterized by sensory, perceptual and cognitive experiences during sleep, usually presenting a strong emotional imprint, and being interpreted as if they were real, i.e., without concern about their bizarreness (Hobson et al., 2000). However, during lucid dreaming (LD), subjects know they are dreaming during the dream, and may control oneiric content (Laberge et al., 1981a; Laberge, 1988), an exception to the rule that dreaming is necessarily an experience concurring with no rational judgment. In Western history, Aristotle's book *On sleep and sleeplessness* is one of the first known references on the possibility of becoming aware of the dream while dreaming. In *The interpretation of dreams* Freud (1900) stated: "... there are people who, during the night, know they are sleeping and dreaming, and then are able to consciously change their dreams". Van Eeden (1913), who coined the term "lucid dream", explains that during this kind of dream "...the reintegration of the psychic functions is so complete that the sleeper remembers day-life and his own condition, reaches a state of perfect awareness, and is able to direct his attention, and to attempt different acts of free volition". More recently, Voss et al. (2013) compared lucid and non-lucid dreams and created a scale based on factors involved in becoming lucid during dreaming: insight, control over thoughts and actions, logical thoughts, access to the mnemonic elements of waking life, and positive emotions.

Neurophysiological studies on LD began with Hearne (1978) and were advanced by Laberge (1980), who developed a technique that consists of instructing subjects to convey an objective signal through ocular movements (e.g., two consecutive left-right turns) (Laberge et al., 1981a) or respiration control (e.g., to breathe rapidly) (Laberge and Dement, 1982) whenever they became lucid while dreaming. This is possible because ocular and respiratory muscles are not in atonia during rapid eye movement sleep

(REMS; Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957), the sleep stage most associated with dreaming (Hobson et al., 2000).

Intriguingly, LD prevalence varies substantially among countries: 26% of a representative sample from Austria ($n = 1{,}000$) reported having a LD at least once in life (Stepansky et al., 1998), while in Germany ($n = 919$), 51% said so (Schredl and Erlacher, 2011). College students in Japan, United States, Holland, Germany and China reported LD prevalences of 47% ($n = 153$) (Erlacher et al., 2008), 71% ($n = 268$) (Palmer, 1979), 73% ($n = 189$) (Blackmore, 1982), 82% ($n = 439$) (Schredl and Erlacher, 2004), and 92% ($n = 348$) (Yu, 2008), respectively. Possible reasons for this discrepancy across studies may rest on the usage of different LD definitions, uncontrolled variability in the volunteers' understanding of these definitions (Erlacher et al., 2008), age differences of the samples (Voss et al., 2012), or variability in other sociocultural aspects, such as the practice of meditation, which is associated with an increased frequency of LD reports (Gackenbach, 1981, 1990; Hunt, 1991).

To our knowledge, there are to date no studies about dream features among Brazilians, nor studies regarding LD prevalence among Latin Americans. Moreover, there is a lack of knowledge regarding LD characteristics in this population, such as number of episodes experienced in lifetime, ability to control oneiric content, episode duration, and facilitating factors of occurrence. It is therefore important to obtain data on these LD features to compare with other populations, or with laboratory studies, such as Laberge et al. (1986), who observed that LD lasted about 2 min in average, but could reach up to 50 min. Thus, to fill this gap, we set out to investigate the characteristics of regular dreaming and LD through an online questionnaire in a sample of 3,427 Brazilian subjects. To facilitate our respondents understanding the difference between lucid and non-lucid dreams, in the present study we used the following sentence: "As bizarre as dreams are, we tend to believe that what is happening during the dream is real. However, during a special kind of dream called lucid dreaming, we are sure to be dreaming during the dream, and we may come to control dream content". The investigation of LD was accompanied by an assessment of general dream features that may influence LD. For instance, remembering more dreams in general is likely to increase the chances of experiencing LD (Laberge and Rheingold, 1990), and therefore we investigated the frequency of dream recall. We further interrogated about bedroom elements that may be incubated in dreams, because incubation of auditory (Laberge et al., 1981b) or visual (Laberge et al., 1988) stimuli into REMS may act as a cue for the subject to become lucid during dreaming. Finally, we investigated recurrent dreams and nightmares, since both may work as a "dream sign", which facilitates dream lucidity (Saint-Denys, 1982; Tholey, 1988; Laberge and Rheingold, 1990; Schredl and Erlacher, 2004).

## MATERIALS AND METHODS

### SUBJECTS

The study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte (permit #061/2008). As stated by the Ethics Committee, all subjects ($n = 3{,}909$) completed an online informed term of consent before completing the questionnaire. Subjects were invited to respond the questionnaire directly by email, or indirectly by online social network services or TV program ads. Subjects who did not answer a given question were excluded from the analysis of this question. We also excluded the subjects who answered less than 90% of the first part of the questionnaire (final sample = 3,427 subjects; median age = 25 years, 56% female and 24% male, 20% did not inform gender) (**Figure 1**). In order to check whether there is an age difference between men and women, we normalized the distributions by the maximum value, and also by $Z$-Score, since many more women answered the questionnaire. Then, the distributions were compared using the Kolmogorov-Smirnov test (controlled by a bootstrap surrogate technique). We also investigated a possible age group effect on the questionnaire responses.

### QUESTIONNAIRE

The questionnaire was divided in two parts: the first part consisted of 10 questions about regular dreams, while the second part involved 10 questions about LD. To facilitate and standardize the subjects' understanding of the difference between lucid and non-lucid dreams, we provided the following explanatory sentence at the onset of the survey: "As bizarre as dreams are, we tend to believe that what is happening during the dream is real. However, during a special kind of dream called lucid dreaming, we are sure to be dreaming during the dream, and we may come to control dream content".

The first part was divided in 4 radio questions (that admit only one answer), 1 check-box question (that admits none, one or more answers) and 5 table questions. These table questions were divided by dream items according to frequency of occurrence: never, very rare (once a year), rare (once a month), frequent (once a week), very frequent (almost every day), and always (every day); for the sake of synthesis, we present the results of the last three answers grouped. The second part of the questionnaire was divided in 7 radio questions, 2 check-box questions and 1 mixed (radio and check-box) question. Details about the original questionnaire can be found at: http://www.cb.ufrn.br/sonho/sonholucidoform.html. A version translated to English is included in the Supplementary Material.

### DATA ACQUISITION AND PRE-PROCESSING

Questionnaires were created using HTML and PHP language and were available to be answered in a website of the Federal University of Rio Grande do Norte.[1] After the questionnaire is filled, the answers were automatically sent to an email account and then converted to MATLAB format. We dropped out 8 questions that were not directly important to our objective, and of the 12 questions that remained, 4 are ordinals—to facilitate correlation analysis interpretation, we transformed all these questions in a direct crescent order.

### DESCRIPTIVE AND CORRELATION ANALYSIS

For dreams (**Figure 2**) and LD (**Figure 3**), we plotted the percentage only for those who answered that specific question (male in white, female in black and "gender not informed" in gray

[1] http://www.cb.ufrn.br/

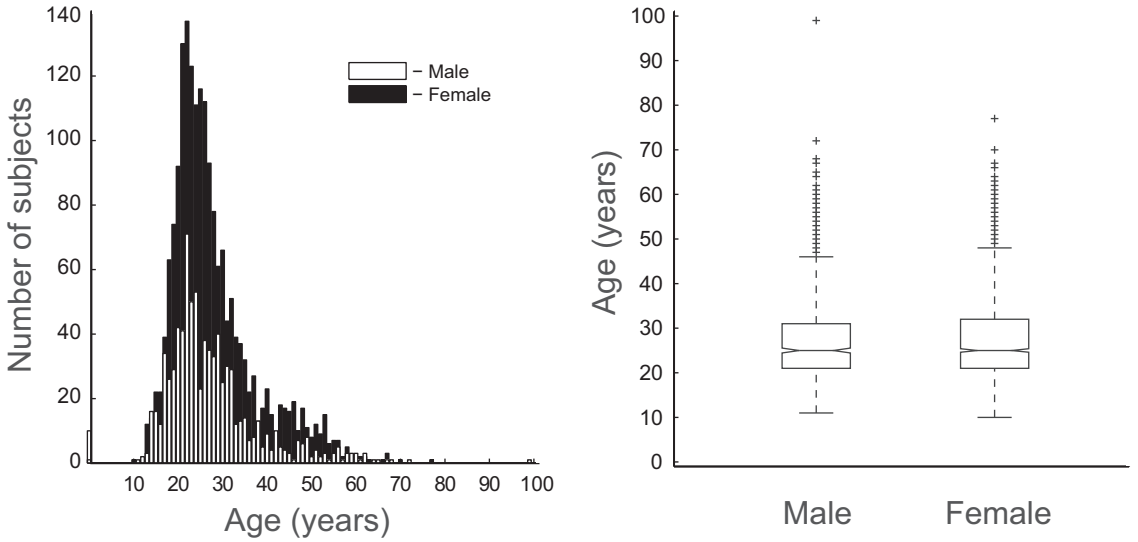


**FIGURE 1 | Epidemiological characteristics of the population sample.** Age distribution (left; white bars = male, black bars = female) and boxplot of ages within genders (right). Outliers indicated by crosses.

bars sum 100%). For ordinal questions (**Figure 4**), we performed a Spearman correlation analysis. Dream recall frequency was measured on a 6-point rating scale: 1 = never, 2 = very rare (once a year), 3 = rare (once a month), 4 = frequently (once a week), 5 = very frequently (almost every day), 6 = always (every day). LD frequency was measured on a 7-point rating scale: 1 = between 1–5, 2 = between 5–10, 3 = between 10–50, 4 = between 50–100, 5 = more than 100, 6 = every week, 7 = almost every day. LD duration was measured on a 6-point rating scale: 1 = very fast, 2 = less than 10 s, 3 = between 10 s–1 min, 4 = between 1–10 min, 5 = more than 10 min, 6 = the time the subject wants. LD control frequency was measured on a 6-point rating scale: 1 = never, 2 = very rare (once a year), 3 = rare (once a month), 4 = frequently (once a week), 5 = very frequently (almost every day), 6 = always (every day).

## RESULTS

### SUBJECTS

3,909 voluntaries responded to the survey, but we excluded those who answered less than 90% of the dream questionnaire (see Section Materials and Methods). In our final sample ($n = 3{,}427$), 56% were female, 24% were male and 20% did not answer the gender. The median age was 25 years (**Figure 1**). Since many more women attended the survey, and in order to investigate whether there is an age difference among gender, we normalized the distributions, and performed a Kolmogorov-Smirnov test, which showed that both distributions are statistically indistinguishable (KS: $H = 0$, $p = 0.2056$). We also investigated a possible age group effect on the responses, but no significant differences were observed.

### DREAM AND NIGHTMARE FEATURES

Subjects who did not answer a given question were excluded from the analysis of this question (see Section Materials and Methods). We found that 34.1% of the subjects remembered dreams frequently (1 or 2 times per week), 33.2% almost every day, 19.8% about twice a month, 9.2% every day, 3.4% once a year and 0.1% less than once a year (**Figure 2A**). With regards to the dreaming point of view, 23.8% of the respondents observe the dream always in first person, 46.2% usually in first person, 11.7% always in third person and 15.3% usually in third person (**Figure 2B**). A total of 37.8% of the subjects reported that their dream was mostly associated with plans for upcoming days and 30.7% claimed that their dreams have nothing to do with them. For 14.2% of the respondents, dreams were associated with the previous day, for 8.8% with the last week, for 4.7% with events that happened for more than one year, for 2.1% with the last year and for 1.8% with the last month (**Figure 2C**).

We also observed that dream content mainly involved movements/actions (93.3%), known people (92.9%), sounds/voices (78.5%), colored images (76.3%), something pleasurable (70.7%) and natural scenes (63.9%). The less common features were unknown people (49.7%), sexual intercourse (30.4%), flying (26.9%), tastes/flavors (26.8%), someone who has died (21.2%), a smell (20.0%), things to read (17.4%), nonexistent creatures (15.0%), black and white images (14.3%) (**Figure 2D**). During nightmares, it is more frequent to experience the presence of anxiety/fear (65.5%), being chased (48.5%), non-painful unpleasant situations (47.6%), psychological threat (39.5%) frustration or failure in a goal (39.1%) and physical threat (35.6%). The less common nightmare features were environmental disasters (21.8%), ghosts/spirits (20.4%), pain sensation, (19.8%), chasing something (15.1%), monsters (13.6%) and wars (9.4%) (**Figure 2E**).

The main sleep room or environmental stimuli that incubate into dreams were the voice of someone (47.6%), phone ring (40.1%), alarm clock (37.5%), house/street noise (37.4%), a tactile sensation (36.2%), TV/radio sounds (32.9%), a light (25.9%), a smell (15.7%) (**Figure 2F**). The recurrent dreams content were mainly associated with a dream with a sensation of being falling

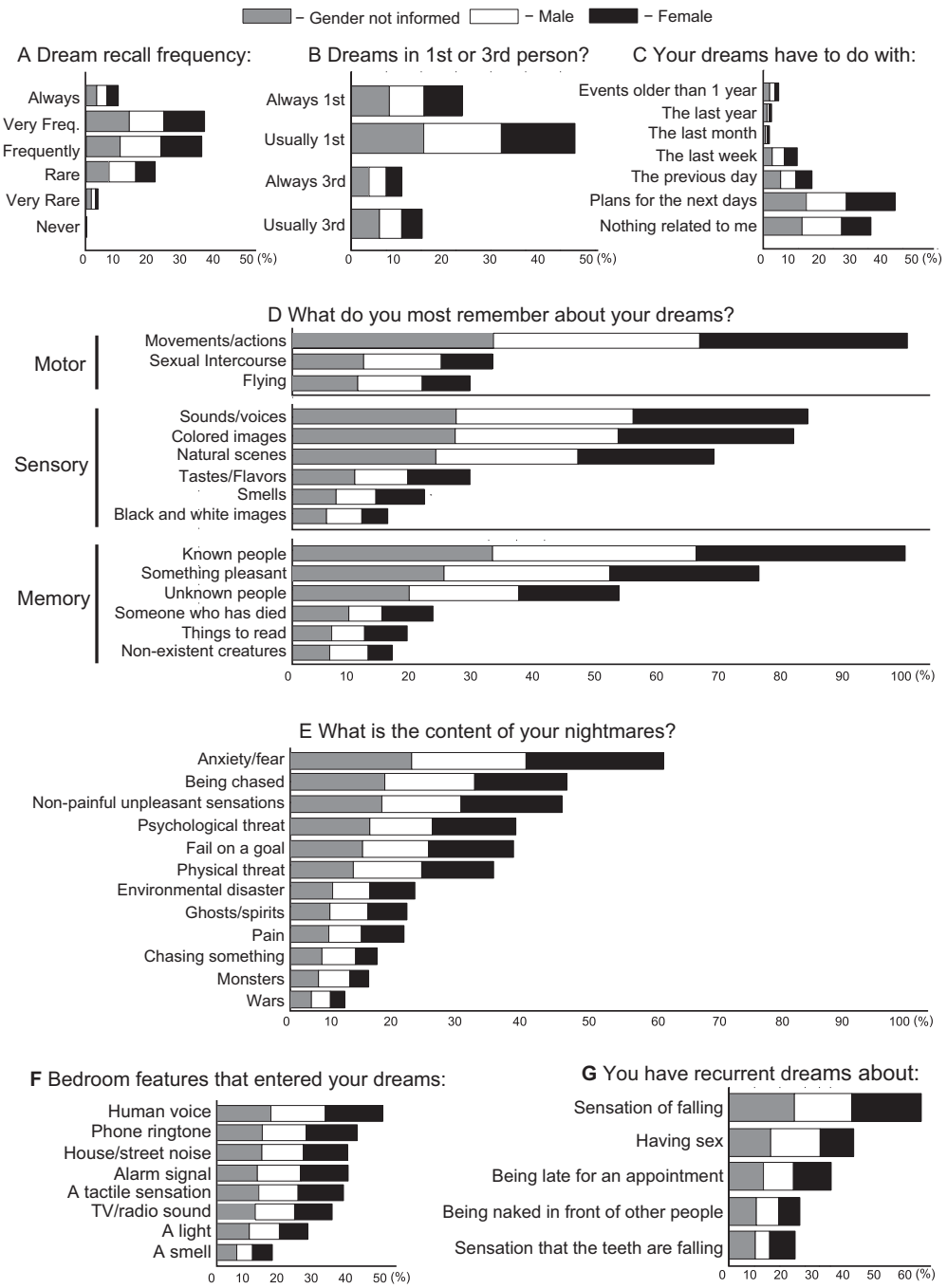


**FIGURE 2 | Frequency and content of dreams and nightmares for female (black), male (white), gender not answered (gray). (A)** Frequency of dream recall. **(B)** Frequency of dream content according to first or third person point of view. **(C)** Dream content according to time: plans, recent or old memories. **(D)** Dream features. **(E)** Nightmares features. **(F)** Sleep environment elements that incubate into dreams. **(G)** Recurrent dream features.

(55.2%), having sex (35.6%), being late for an appointment (29.2%), being naked in front of people (20.2%) and feel the teeth falling out (18.8%) (**Figure 2G**).

## LUCID DREAMING FEATURES

We observed in our sample that 77.2% of the subjects had already experienced at least one LD episode in their whole lifetime (**Figure 3A**). With respect to the number of LD episodes, 27.2% had experienced between 10–50 episodes, 22.8% between 1–5, 22.1% between 5–10, 12.2% have LD every week, 6.6% had between 50–100, 4.8% had more than 100 episodes, and 3.9% have LD almost every day (**Figure 3B**). With regards to the frequency of controlling LD content, 29.7% of the respondents control LD rarely, 29.3% frequently, 18.8% very frequently, 12.0% very rare, 6.4% always and 3.6% never (**Figure 3C**). Whenever subjects are able to control LD, 47.6% choose to visit different

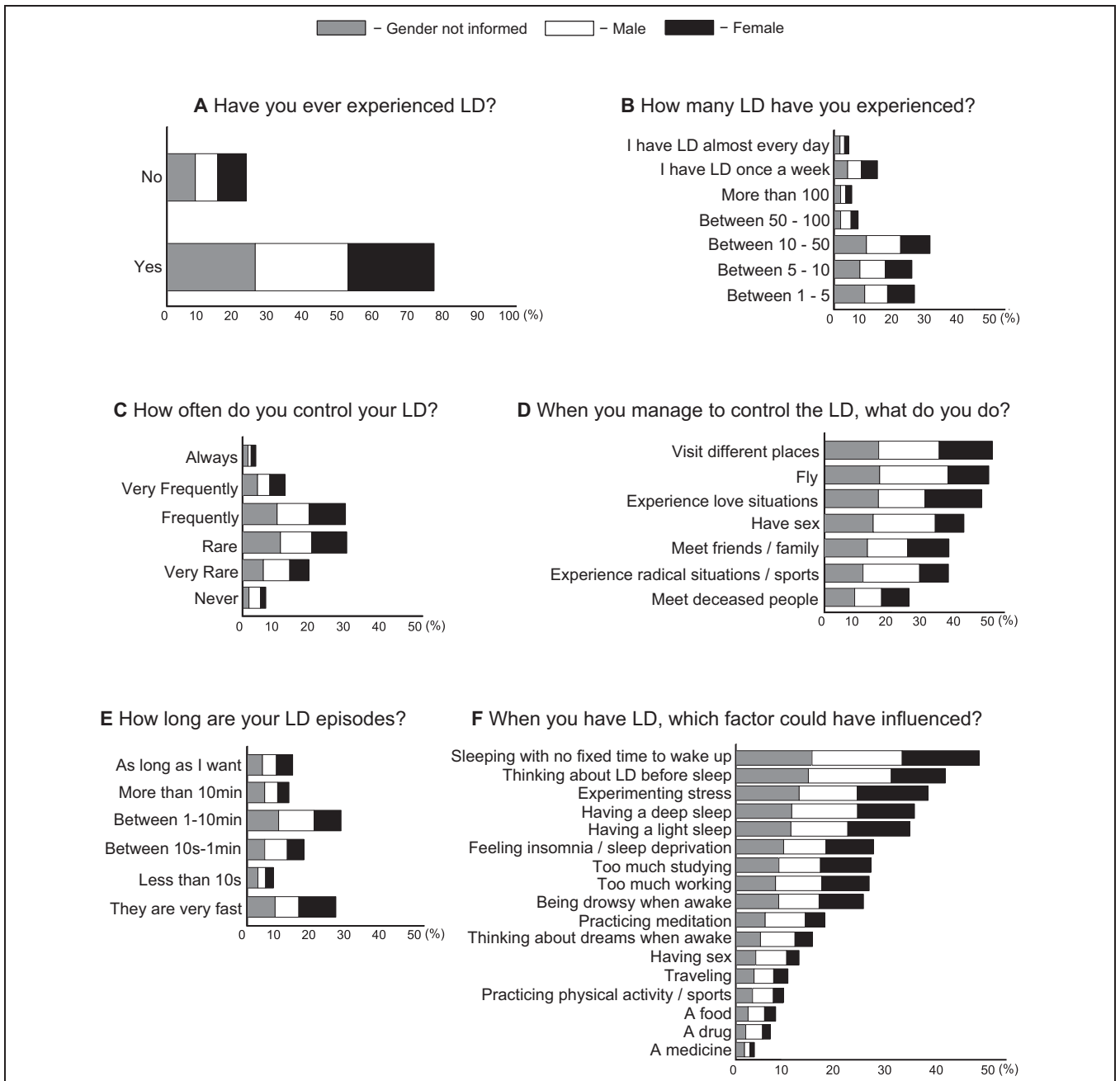


**FIGURE 3 | Frequency and content of LD for female (black), male (white), gender not answered (gray).** (**A**) Percentage of LD report for at least once in lifetime. (**B**) Number of LD episodes recall. (**C**) Frequency of LD control. (**D**) Things to do during LD. (**E**) LD episodes duration. (**F**) Factors that may have facilitated LD occurrence.

places, 46.7% to fly, 44.6% to experience love situations, 39.5% to have sexual intercourse, 35.3% prefer to meet friends, 35.2% to experience radical situations, and 23.9% to meet deceased people (**Figure 3D**).

With respect to LD episode duration, 26.7% report that LD takes between 1–10 min, but 25.2% tend to wake up after realizing the LD. For 16% LD takes between 10 s and 1 min, and for 12.8% LD takes the time the dreamer wants. For 11.7% LD takes more than 10 min and for 7.3% less than 10 s (**Figure 3E**). The facilitating factors for LD occurrence were related to: sleep without a fixed time to wake up (38.3%), think about LD before sleep (32.8%), experiencing stress (30.1%), have a deep (28.1%) or a light sleep (27.3%), insomnia (21.5%), too much study (21.1%), too much work (20.9%), be sleepy when awake (20.0%), practice meditation (13.9%), think about dreams during waking (11.9%), have sex (9.3%), travel (8.1%), practice physical activity (7.3%), a food (6.1%), a drug (5.3%), a remedy (2.8%) (**Figure 3F**). LD frequency was positively correlated with dream

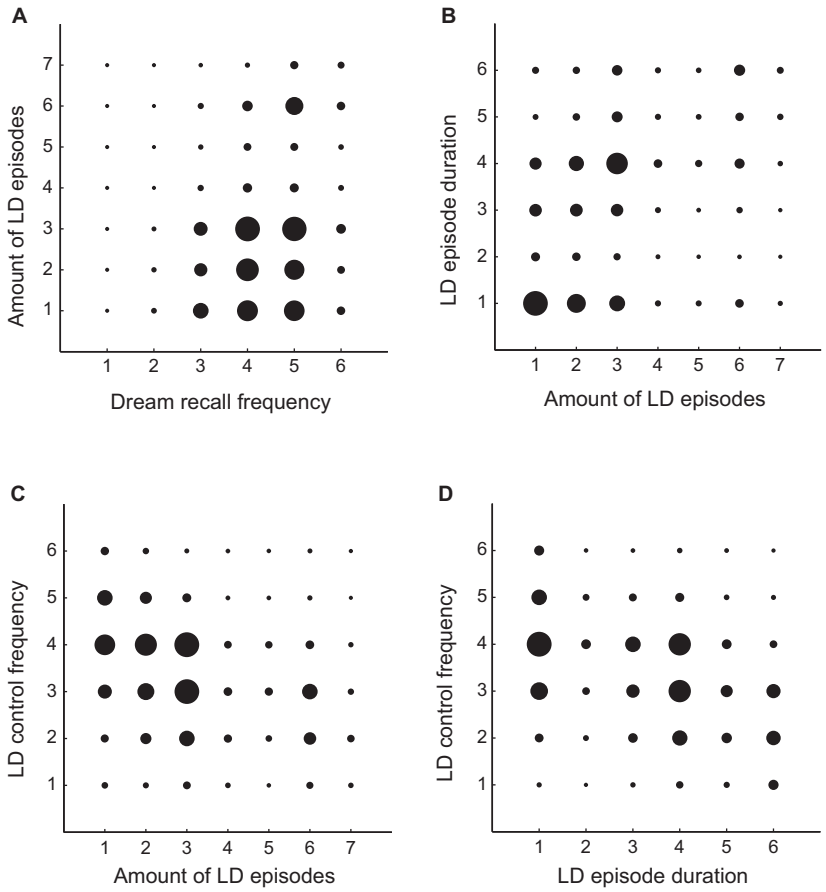


**FIGURE 4 | Correlations between dreaming and LD features.** (**A**) Amount of LD episodes and dream recall frequency ($r = 0.20$, $p < 0.01$). (**B**) Amount of LD episodes and LD episode duration ($r = 0.34$, $p < 0.01$). (**C**) Amount of LD episodes and LD control frequency ($r = -0.33$, $p < 0.01$). (**D**) LD control frequency and LD episode duration ($r = -0.38$, $p < 0.01$). The size of the black circles is associated with the number of subjects that responded to the pair of answers for both questions. The amount of LD episodes were measured on a 7-point rating scale: 1 = between 1–5, 2 = between 5–10, 3 = between 10–50, 4 = between 50–100, 5 = more than 100, 6 = every week, 7 = almost every day. Dream recall frequency was measured on a 6-point rating scale: 1 = never, 2 = very rare (once a year), 3 = rare (once a month), 4 = frequently (once a week), 5 = very frequently (almost every day), 6 = always (every day). LD episode duration was measured on a 6-point rating scale: 1 = very fast, 2 = < 10 s, 3 = 10 s–1 min, 4 = 1–10 min, 5 = > 10 min, 6 = the time I want. LD control frequency was measured on a 6-point rating scale: 1 = never, 2 = very rare, 3 = rare, 4 = frequently, 5 = very frequently, 6 = always.

recall frequency ($r = 0.20$, $p < 0.01$—**Figure 4A**), with LD episode duration ($r = 0.34$, $p < 0.01$—**Figure 4B**) and negatively with LD control frequency ($r = -0.33$, $p < 0.01$—**Figure 4C**). LD control frequency was negatively correlated with LD episode duration ($r = -0.38$, $p < 0.01$—**Figure 4D**). LD report (at least once in lifetime) was most common in male (75%) than in female (68%) ($\chi^2 = 10.2$, $p = 0.001$).

## DISCUSSION

One important limitation of our study, intrinsic to an online survey, is the lack of information about the physiological state underlying each dream report. Dreams are not restricted to REMS (Hobson et al., 2000; Solms, 2000), and therefore the data collected likely reflect a mix of consciousness states. Irrespective of this caveat, we observed that dream reports were mainly related to plans for the next days, but were also associated with memories of the previous days, months or years (**Figure 2C**). Nightmare reports dealt mainly with situations somewhat likely to occur in everyday life, such as experiencing anxiety and fear, being physically/psychologically threatened, and feeling unpleasant sensations or frustrations; in contrast, unlikely events such as suffering environmental disasters, meeting non-existent creatures such as monsters, ghosts or spirits, chasing someone/something, or being in a war were less reported as nightmare contents (**Figure 2E**). While these results seem to support the notion of day residue (Freud, 1900), the hypothesis is limited by the fact that pain, a relatively common wake experience, is not frequent in dream records, as found by Zadra et al. (1998b) and also here (**Figure 2E**). On the other hand, the results are more compatible with the theory that nightmares (Revonsuo, 2000), and perhaps all dreams (Ribeiro and Nicolelis, 2006; Mota-Rolim and Araujo, 2013), constitute adaptive behavioral simulations related to the social, psychological and biological fitness of the dreamer. Specifically

regarding LD, we observed that it is relatively ubiquitous although infrequent, unstable, and difficult to control (**Figure 3**). Adding Latin American data to prior assessments of LD prevalence among North Americans (Palmer, 1979), Europeans (Blackmore, 1982; Stepansky et al., 1998; Schredl and Erlacher, 2004, 2011) and Asians (Erlacher et al., 2008; Yu, 2008), our results strengthen the notion that LD is a general phenomenon of the human species.

We initially investigated non-lucid dreams, and observed that most respondents claimed to remember dreams once or twice a week (**Figure 2A**), in accordance with similar studies on dream recall frequency (Herman and Shows, 1983; Schredl et al., 2003; Nielsen et al., 2006). The dream content, according to subjective point of view, was classified as first person dreams (active dreams "from within", in which the subject makes decisions and acts at will), or as third person dreams (passive dreams, in which the dreamer participates "from without" as an observer, spectator or just another dream character). We found that subjects tended to dream more in first person than in third person (**Figure 2B**), indicating that self-consciousness is preserved in most dreams. We also observed that dreams were related to memories of previous days, weeks, months and even years (**Figure 2C**), which is in accordance with Freudian theory of "day residue" (Freud, 1900). Surprisingly, dreams associated more with plans for the next day, suggesting that the oneiric content relates with simulations of future scenarios (Revonsuo, 2000). However, about one third of subjects reported that their dreams had nothing to do with their lives (**Figure 2C**), supporting the existence of stochastic influences over dreaming (Hobson and McCarley, 1977; Foulkes, 1985; Hobson et al., 2000), which restructure memory traces so strongly that mnemonic activation ends up not being recognizable by the dreamer (Ribeiro and Nicolelis, 2006).

The general dream content (**Figure 2D**) mainly involved movements and actions, known people, colored images and sounds/voices, in accordance with previous studies (McCarley and Hoffman, 1981; Zadra et al., 1998a) and likely reflecting the sensorimotor repertoire of our daily life. Smells are unlikely to be present in dreams (**Figure 2D**), which is in accordance with Hobson et al. (2000). Reading was also rare during dreams (**Figure 2D**), which could be due to a low blood flow in the frontal cortex during REMS (Maquet et al., 1996) that may impair attention (Tsakiris et al., 2007) and working memory related tasks (Baddeley, 1992; Hobson and Stickgold, 1994; Revonsuo and Salmivalli, 1995; Baddeley and Della Sala, 1996; Hobson, 1997; Courtney et al., 1998).

During nightmares (**Figure 2E**), subjects reported mainly anxiety and fear, which is in accordance with a previous study (Merritt et al., 1994). Other frequent nightmare contents were being stalked, frustration or failure to reach a goal, and psychological or physical threat, in this order of prevalence. The less common nightmares were related to environmental disasters, ghosts, feeling pain, chasing something/someone, monsters and war, respectively. The threat-simulation theory proposed by Revonsuo (2000) postulates that dreams and nightmares are meant to simulate situations that can happen in the real world. This is corroborated by the observation that all sensory modalities are present in dreams with a frequency comparable to that of wakefulness, according to Zadra et al. (1998a) and also observed here (**Figure 2D**). Emotions during dreaming are mainly fear or anxiety (Snyder, 1970), as found here (**Figure 2E**). Aggression is the most frequent form of social interaction during dreaming, and dreamers are primarily victims (Hall and Van De Castle, 1966). Consistent with this, we also observed that it is much more common to being stalked than to chase something or someone (**Figure 2E**). The limbic activation during REMS, especially in the amygdala (Maquet et al., 1996; Braun et al., 1998) would be the neural correlate of threat-simulation (Revonsuo, 2000).

To Revonsuo (2000), the threat-simulation theory is based on the fact that the prehistoric environment—in which the human brain evolved—included frequent dangerous events, such as animals' and/or other human groups' threats in competition for territory or food, which challenged the reproductive success of the hunter-gatherers, and therefore represented important selection pressures on those populations. This is observed by the increased presence of such content in young children dreams (whose brain has not had a chance to adjust to contemporary society) and its gradual decline into adulthood (Strauch, 1996). Gregor (1981) analyzed the content of 385 dream reports obtained among the Mehinaku Indians (from Brazil), and observed that their dreams contained significantly more physical aggression (mostly from animals) in comparison with a sample of townspeople. A similar result was observed by Calvin Hall in the early 1930's, among the Yir Yoront, a native population of Australia (*apud* Domhoff, 1996).

We further investigated the environmental stimuli in the sleeping room able to incubate into dreams. The most reported sensory modality to enter dreams was the auditory one, such as the voice of someone, phone ring, alarm clock, and house or street noise; the less frequent were tactile stimuli, light and smells (**Figure 2F**), which is in accordance with previous studies (Freud, 1900; Laberge et al., 1981b, 1988; Carskadon and Herz, 2004). With regard to recurrent dreams, we observed that the most reported content was dreaming with the sensation of falling (**Figure 2G**), which may be attributed to a rapid decline in muscle tone during sleep (or REMS) onset. Having sex, being late for an appointment, or being naked in front of other people are frequent contents (**Figure 2G**), perhaps because desires and fears play a major role in shaping dreams (Freud, 1900; Revonsuo, 2000). Another frequent content of recurrent dreams is teeth loss, in line with previous reports (Schredl et al., 2004; Zadra et al., 2006). The explanation for this kind of recurrent dream remains speculative: Lorand (1948) believes that it is associated with masturbation in men, parturition in women or regression to childhood, while Schneck (1956, 1967) postulates a link with the fear of growing old (*apud* Schredl et al., 2004).

Regarding LD, we observed that 77,2% of our sample already had experienced LD at least once in lifetime (**Figure 3A**). However, LD prevalence varies substantially among different populations, ranging from 26% (Stepansky et al., 1998) to 92% (Yu, 2008). We believe that two factors may contribute to the discrepancy in LD prevalence across studies: (1) researchers provided different definitions of LD to the respondents, and (2) the LD concept itself is difficult to understand, especially for those who are not used to remember or talk about dreams. In our study, the

questionnaire was applied through the internet; to minimize this limitation, we tried to provide a clear definition of LD (see Section Materials and Methods). Moreover, LD questions came only after the questions about non-lucid dreaming; this may have helped subjects to better understand the differences between these kinds of dream (see Supplementary Material). It should be noted that this relatively new field still lacks a consensual standard on the definition of Lucid Dreaming. The study by Voss et al. (2013), which investigated consciousness features during dreaming, was published after our data was collected, and thus we could not use their comprehensive LD definition in our survey. We also believe that epidemiological characteristics of the analyzed populations may explain the different prevalence of LD in distinct samples, such as age (Voss et al., 2012) and meditation practice (Gackenbach, 1981, 1990; Hunt, 1991), for example.

We found a correlation between dream recall frequency and LD frequency (**Figure 4A**), which is in accordance with previous studies (Blackmore, 1982; Wolpin et al., 1992; Schredl and Erlacher, 2004, 2011; Voss et al., 2012). In accordance, Laberge and Rheingold (1990) argue that remembering more dreams in general should increase the chances of remembering LD. In the present study, we observed that LD was more frequent among males than females. Most studies reported no differences in LD frequency between genders (Gruber et al., 1995; Stepansky et al., 1998; Schredl and Erlacher, 2004), but one study reported that LD recall was higher in women (Schredl and Erlacher, 2011). In our survey, women were much more participative (**Figure 1**), and it is possible that the men who answered the questionnaire were on average more likely to have experienced LD than the general male population, which could have biased our results.

The report of having experienced at least one LD episode was frequent (**Figure 3A**), but at the same time LD was largely non-recurrent; most of the people had less than 10 episodes in their whole lifetime (**Figure 3B**). Based on the observations that LD occurs predominantly during REMS (Brylowski et al., 1989; Laberge and Rheingold, 1990) and most people present REMS every night, an intriguing issue is why LD is so uncommon. We have previously proposed that a likely explanation for this discrepancy is that there exists more than one kind of REMS, and that the specific kind of REMS during which LD occurs is rare, with EEG spectral features that differentiate it from non-lucid REMS (Mota-Rolim et al., 2010). Consistent with this, early studies reported that the level of lucidity relates to the overall power in the alpha band (8–12 Hz) (Ogilvie et al., 1982; Tyson et al., 1984). However, more recent work found increased EEG power within the beta band in the parietal area (Holzinger et al., 2006), and the gamma band (peaking around 40 Hz) in the frontal region during LD (Hobson, 2009; Voss et al., 2009). Using cognitive tasks and a dream diary, Neider et al. (2011) observed that subjects who performed better on a task that engages the ventromedial prefrontal cortex exhibited more lucidity reports. This was not true for a task related to the dorsolateral prefrontal cortex (Neider et al., 2011). Therefore, there is evidence to suggest that LD present different spectral characteristics than non-LD, despite the disagreement with regard to the brain regions and frequency bands most related to LD. We recently suggested that different subjective experiences during LD could have different underlying neural substrates (Mota-Rolim et al., 2010). In accordance, Dresler et al. (2011) observed that performing hand movements during LD specifically elicits neuronal activation in the sensorimotor cortex.

We also observed that it is difficult to achieve full volitional control of LD (**Figure 3C**), which is typically ephemeral—the majority of our sample reported that LD subjective duration was below 1 min (**Figure 3E**). A laboratory-based study with experienced lucid dreamers found that LD (verified by eye-movement lucidity signal) lasted an average of 115 s (range from 5 s to 490 s), up to 50 min in length (Laberge et al., 1986). Although the data on LD duration is problematic, given the known distortion of time perception during dreaming, Dement and Kleitman (1957) described a temporal correspondence between dream and waking events. In this study, participants were randomly awoken 5 or 15 min after the onset of REMS. After waking up, subjects were asked whether they had dreamed for 5 or 15 min: in a total of 111 awakenings, the correct time estimation was observed in 83% of the reports. Other studies found similar results, such as Glaubman and Lewin (1977), and Hobson et al. (2000). Recent studies have suggested that time perception in LD is similar to wakefulness, but motor activity is slower (Erlacher and Schredl, 2004). We also found a negative correlation between LD control and LD duration (**Figure 4D**), suggesting that when subjects try to control LD they tend to wake up.

The factors that facilitated LD occurrence (**Figure 3F**) were related to sleep and dream features (e.g., sleeping without a fixed time to wake up, thinking about having a LD before sleeping, thinking about dreams during the day), negative stimuli (stress, too much study, too much work, or insomnia), positive stimuli (meditation practice, sexual intercourse, traveling, physical activity), among others (drug use, food intake). Consistent with our data, Laberge and Rheingold (1990) also observed that thinking about having a LD before sleeping may induce LD, indicating that LD occurrence is susceptible to suggestion. Sleeping without a fixed time to wake up may facilitate LD because it is associated with REMS (Brylowski et al., 1989), the sleep stage more related to dreaming (Hobson et al., 2000), which is prevalent in the last hours of sleep (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957). Stressful factors such as insomnia, sleep deprivation, excessive study and/or work, were also facilitating factors (**Figure 3F**). This could be due to an increase of REMS transitions into the waking state associated with stress (Kim and Dimsdale, 2007), which would support the hypotheses that LD could happen in the transition phase from REMS to waking. The important incidence of such transitions is pointed by Mahowald et al. (2011): "...even in normal subjects, the electrographic and neuronal activity transitions among states are gradual and variable, with the simultaneous occurrence or rapid oscillation of multiple state-determining markers indicating ongoing variability and fluctuation of state determination underscoring the fact that sleep is not a global, whole brain phenomenon".

We confirmed the observation that meditation practice increases LD frequency (Gackenbach, 1981, 1990; Hunt, 1991; **Figure 3F**). A previous study found that long-term meditation

practitioners have increased rapid eye movement density during REMS (Manson et al., 1997), which could be related to a higher LD frequency in these subjects. However, for Ogilvie et al. (1982), LD and meditation would be related by the increased power in the alpha band (8–12 Hz) observed in both mental states. Other authors believe that this correlation is associated with a greater mental control, which would emerge in both meditation practitioners and frequent lucid dreamers (Blagrove and Tucker, 1994; Blagrove and Hartnell, 2000). Buddhist monks from Tibet also developed the so-called "dream yoga": this meditation technique is based on cognitive-behavior methods to induce LD direct from wakefulness (Laberge, 2003). We have not found references in literature with respect to others factors that facilitate LD occurrence.

To conclude, we believe that dreams may have acquired an adaptive function, acting as a simulation of the past (associated with memory), or the future (associated with plans and expectations) (Ribeiro and Nicolelis, 2006). From this point of view, dreams are mainly related to two forces: wishes, as Freud (1900) postulated, but also fears (Revonsuo, 2000). These are the elementary tenets of evolution: based on past experiences we desire the pleasant, but are also afraid of taking risks (Mota-Rolim and Araujo, 2013). As a special type of dream, our results indicate that LD is relatively common but not recurrent, often elusive and difficult to control. About three quarters of the Brazilian subjects in our sample reported having experienced at least one LD in their lifetime. Despite the variable prevalence of LD among different populations in Europe, Asia, North and now South America, our data strengthens the idea that LD is a general phenomenon of the human species. Since LD has been neglect by most neuroscientists and psychoanalysts, our results may call their attention to this important phenomenon.

Having performed an internet survey about dreaming, we are aware of the intrinsic methodological limitations of data reliability. First, it has no supervision and is prone to respondents' exaggerations and/or understatements. Second, responses were collected through an online survey, thus yielding a biased sample, at the very least restricting it to people with internet access. Thus the conclusions drawn from our survey should not be taken at face value as representative of the whole population. It is also important to point out that since our study was not a laboratory-based dream investigation, we dealt with dream reports and what is remembered of them—not dream content collected immediately after awakening—especially because we asked for reports on dream content covering a wide time range, without distinction between recent and remote dreams. Other limitations include no data on subject occupation and LD entry state (from waking or from dreaming) (Laberge, 1988). Finally, it is important to point out that REMS dreams and LD are likely to be confounded with other states of consciousness not addressed in this survey, such as: (1) the physiological transition from the waking state to dreaming, and from dreaming to the waking state (hypnagogic and hypnopompic hallucinations, respectively); (2) during altered mental states such as hypnosis, trance etc.; and (3) pathologically, as in REMS behavior disorder and sleep paralysis, among others (Mahowald et al., 2011).

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnhum.2013.00836/abstract

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# Trauma, dream, and psychic change in psychoanalyses: a dialog between psychoanalysis and the neurosciences

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To many psychoanalysts dreams are a central source of knowledge of the unconscious—the specific research object of psychoanalysis. The dialog with the neurosciences, devoted to the testing of hypotheses on human behavior and neurophysiology with objective methods, has added to psychoanalytic conceptualizations on emotion, memory, sleep and dreams, conflict and trauma. To psychoanalysts as well as neuroscientists, the neurological basis of psychic functioning, particularly concerning trauma, is of special interest. In this article, an attempt is made to bridge the gap between psychoanalytic findings and neuroscientific findings on trauma. We then attempt to merge both approaches in one experimental study devoted to the investigation of the neurophysiological changes (fMRI) associated with psychoanalytic treatment in chronically depressed patients. We also report on an attempt to quantify psychoanalysis-induced transformation in the manifest content of dreams. To do so, we used two independent methods. First, dreams reported during the cure of chronic depressed analysands were assessed by the treating psychoanalyst. Second, dreams reported in an experimental context were analyzed by an independent evaluator using a standardized method to quantify changes in dream content (Moser method). Single cases are presented. Preliminary results suggest that psychoanalysis-induced transformation can be assessed in an objective way.

**Keywords: psychic trauma, dreams, psychoanalysis, neurosciences, EEG-fMRI**

## INTRODUCTION

In 2006, declared as "the Year of Freud," one could easily get the impression that the dialog between psychoanalysis and the neurosciences was the most important window that opened modern day psychoanalysis to the world of contemporary scientific discourse. Can we, as psychoanalysts, initiate a fruitful dialog with neuroscientists and gain additional knowledge of the unconscious, psychoanalysis' specific research object?

Throughout his entire life Freud had hoped that new developments in the neurosciences would contribute to exploring psychoanalytic processes from a natural scientific point of view. In many of his historical and theoretical papers the South African neuropsychologist and psychoanalyst Mark Solms substantiates that Freud—due to the standard of neuroscientific methods during his time—turned his back on this vision and defined psychoanalysis as a solely psychological science of the unconscious. Over the past few years, recent developments in the neurosciences, e.g., investigating the living brain with the help of neuroimaging techniques, as well as the neuro-anatomic method, as described by Solms and other psychoanalytic researchers, have stimulated and intensified the interdisciplinary dialog between psychoanalysis and the neurosciences. The first issue of the international journal "Neuro-Psychoanalysis" was printed in 1999, featuring well-known neuroscientists and psychoanalysts controversially discussing in detail topics such as emotion, memory, sleep and dreams, conflict and trauma, as well as conscious and unconscious problem-solving processes. The international Society for Neuro-Psychoanalysis was founded in the year 2000 contributing to an exchange between both scientific disciplines via regular congresses.

Apparently a growing number of worldwide research groups have begun to realize that the neurosciences and psychoanalysis can benefit from each other in interesting ways. By now the neurosciences are equipped with objective and precise methods of verifying hypotheses about human behavior, while psychoanalysis, based on its rich experience with patients and its unique method of field research has developed a variety of different models in order to conceptualize the multi-layered and complex observations derived from the psychoanalytic situation and to test them by means of its specific form of empirical research—clinical psychoanalytic research. Psychoanalysis' explanatory models and insights can conversely be of interest to neuroscientists and raise specific research questions (see e.g., Fischmann et al., 2012a; Ruby, 2013).

Sometimes also empirical studies evoke challenging research questions for both research fields. In the on-going LAC-Depressionstudy (see below), for example, one interesting and unexpected finding for both research fields is that a large majority of chronically depressed in long-term psychoanalytic therapy suffered from severe traumatization during childhood. The scientific discourses on the long-term effects of traumatizing experiences can be traced back to the mid 19th century (Sachsse et al., 1997; Bohleber, 2000b, 2010; Mertens and Waldvogel, 2008) when Freud developed his first theoretical understanding of

trauma in 1895 in his "Project for a Scientific Psychology" (Freud, 1950[1895]). In the 1920s he developed the structural model of psychoanalysis, a "solely psychological" theory. Nevertheless, as is well known, Freud always kept his interest in the neurological basis of psychic functioning, particularly also concerning the topic of trauma.

After World War II the consequences of "man-made disasters" refocused the professional attention on trauma. For one, the extremely traumatizing experiences of the Holocaust, which led many survivors to reach out to psychoanalysts in the form of treatment or for an assessment due to reparation claims, compelled a reviewed analysis of the short- and long-term consequences of extreme traumatization. Moreover, the treatment of survivors' children conveyed the insight that traumatic experiences of this enormity also encroach on the lives of the following generations. "Man-made disasters" have various transgenerational effects, not only for the directly involved families, but also for society as a whole and for the trauma's representation within the collective memory and group identity, subjects for further interdisciplinary dialog (Bohleber, 2000a, p. 795, 2010) [1]. Many decades ago, Hans Keilson (1979), amongst others, characterized Auschwitz as a place "which our language cannot reach," where the traumatic experience destroyed the human shield that is the structure of meaning. The traumatic experience carves itself into the body and directly influences the organic base of psychic functions. Psychic space and the ability to symbolize are destroyed (Laub et al., 1995; Bohleber, 2000b, 2010; Kogan, 2002). These findings from clinical psychoanalytic research have been pursued by many psychiatric and neurobiological researchers in the last years (see following section).

## PSYCHOANALYTIC AND NEUROBIOLOGICAL TRAUMA RESEARCH

In any age traumatization can lead to severe incursions of a person's psychic structures (also see Leuzinger-Bohleber, 2010, 2013; Leuzinger-Bohleber et al., 2010). One of the effects of an acute, severe traumatization is that the affected person is abruptly seized from reality by the traumatic experience: within a dissociated condition he now experiences the reality surrounding him in a completely different way, unreal, fey, separated from all other people, isolated and lonely. Intuitively he realizes that this experience depicts an infraction in his life that he will carry within himself from now on. Nothing will be as it was before. Psychoanalysts know by treating severely traumatized patients that they did not find their way back into their old lives after such an experience: psychically they are "never totally present," they have permanently lost their foothold, feel disconnected toward others and never regain the sense of being the active center of their own lives.

These psychoanalytic insights on the psychodynamics and genesis of traumatization are generally based on psychoanalysts' intense work with individual patients seeking relief from their psychic or psychosomatic problems. Most often the insights about unconscious determinants of psychic grief not only turn out to be "healing" pertaining to the physical symptoms but also in a meaning-giving way, in the sense that certain, until now, unknown effects of sustained traumatization are now recognized as memories or memorials of the personal, distinctive life story and psychically integrated.

In contrast psychiatric and neuroscientific literature debate trauma centered on "posttraumatic stress disorder." The DSM-IV definition of posttraumatic stress disorder (PTSD) is regarded as the international standard and its definition has become the basis of many interdisciplinary studies. It must be taken into account that this definition is solely descriptive in nature, and does not give an account about which psychic and/or neurobiological mechanisms lie at the root of this psychic traumatization. In terms of the DSM-IV, posttraumatic stress disorder is "the development of characteristic symptoms after being exposed to a traumatic event." This event is defined as: "The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others." (DSM Criteria for PTSD). Such an event impacts the subject in the form of an external, massive stressor and changes the structural features which have been formed in part by genetics, prenatal and early childhood attachment, and experiences in the outside reality. This impact is identified as a threat by the brain and therefore quickly leads to a somatic stress reaction accompanied by severe psychic reactions (cf. Sachsse and Roth, 2008; Reinhold and Markowitsch, 2008).

Among others, DSM-IV lists the following symptoms for PTSD: intense fear, helplessness or horror, recurrent and intrusive distressing recollections of the event, persistent avoidance of stimuli associated with the trauma, as well as persistent symptoms of increased arousal. The causes for traumatising situations are e.g., wars, natural disasters, severe accidents, as well as harm caused by others such as torture or rape" (DSM-IV, p. 487).

What consequences do these different approaches have for the treatment of traumatized individuals? From a psychoanalytic point of view today, in cases of traumatic experiences the natural stimulus barrier is interrupted by unforeseen, extreme experiences, usually linked to a threat to life or mortal fear. The ego is exposed to an extreme feeling of powerlessness and inability to control or manage the situation and is therefore flooded with panic and extreme physiological reactions. The flooding of the ego leads to a psychic and physiological state of shock. The traumatic experience also destroys the empathic shield of the internalized primary object, the confidence in the constant presence of good objects, and the expectancy of human empathy. In trauma the inner, good object, the negotiator between self and surroundings becomes mute (Hoppe, 1962; Cohen, 1985). The feeling of continuity and the basic sense of one's own life are lost.

[1] To this day psychoanalytic literature is struggling to achieve an adequate understanding of trauma. Bohleber (2010, p. 21) recently summarized the current state of knowledge as follows: "Psychoanalytic trauma theory have evolved on the basis of two models, one psycho-economic, the other hermeneutic based on object relations theory. To grasp the phenomenology and long-term consequences of trauma, we need both models. The psycho-economic model focuses on excessive arousal and on anxiety that cannot be contained by the psyche and that breaks through the shield against stimuli. The model based on object relations theory concentrates on the collapse of internal object relations and the breakdown of internal communication, which produces an experience of total abandonment, precluding the integration of trauma by narrative means."

Therefore the "narrative," and the "meaning-giving" psychotherapeutic dimension are essential for treating the group of severely traumatized persons. At the same time psychiatric and neuroscientific findings on the brain function of traumatized patients may be relevant even for psychotherapists, as we try to illustrate in this paper.

Hence in our introduction we try to bridge the gap between psychoanalytic and neuroscientific findings on trauma. In the next section we apply this knowledge to an on-going study by simultaneously examining chronically depressed patients with EEG and fMRI during their psychoanalytic treatment. Our example of a single case study will illustrate in the last section how a change of manifest dream contents, as they are portrayed in psychoanalytic sessions, can be contrasted by changes in the contexts of dreams in the sleep laboratory. As we have discussed in previous works, within the transference relationship with the analyst when dealing with severely traumatized, depressive patients, it is inevitable that the traumatic experience is revived and thus understood in detail in its biographical ("historical") dimension (Fischmann et al., 2012a; Leuzinger-Bohleber, 2013). Only then does trauma in its enclosed, psychic existence become accessible to therapeutic work: the unutterable horror is linked to visualizations, metaphors and eventually to verbalizations. Dreams are often helpful in this context: many analysands convey indicators for an incipient symbolization process and the conclusive onset of "meaning-giving" therapeutic coping with the traumatization. Therefore the changes of dreams during psychoanalysis with severely traumatized patients could indicate that a symbolization process of the trauma has taken place—and thus indicating significant transformations in the inner world of the patient. In this paper we would like to report on an attempt to measure such transformation processes in the manifest dreams of chronic depressed analysands not only by clinical psychoanalytic observations but also by a theory-guided content analysis of dreams developed by Moser and von Zeppelin (1996) that is accepted by the non-psychoanalytic academic community. In this model the state of the art of experimental and neurobiological dream/sleep research has been integrated.

## DREAM AND DEPRESSION

In dream research dreaming is described as a thought-process in which our inner system is engaged in processing information (Dewan, 1970). Inner (cognitive) models are constantly being modified in coordination with what is perceived. In contrast to dreaming reactions to our environment are immediate during the waking state, thus enabling information consolidation into memory only limited by capacity restrictions of the system itself. Nevertheless, consolidation processes do continue during sleep in an "off-line" modus, thus enabling integration into the long-term memory here as well (Stickgold and Walker, 2007).

According to Moser and von Zeppelin[2] (1996), both psychoanalysts and dream researchers, the so-called "dream complexes," activated by current events, process the entirety of information deriving from unsolved conflicts and traumatic situations while dreaming. The dream searches for solutions or rather best possible adaptations for these dream complexes. A dream, which is usually pictorial, consists of at least one situation produced by a "dream-organizer." Dream-organization may be considered—according to Moser—as a bundle of affective-cognitive procedures, generating a micro-world—the dream—and controlling its course of action. Within this system the "dream-complex" is a template facilitating dream organization.

Thus, it may be assumed that a "dream-complex" originates from one or more complexes stored in the long-term-memory, rooted in conflictuous and/or traumatizing experiences, which found their condensates in *introjects*. These introjects are closely related to triggering stimuli from the outside world and structurally similar to stored situations of the complex. The searched for solution of the complex is governed by the need for security and the wish for involvement, i.e., the *security-principle* and the *involvement-principle,* managing the dream-organization. Wishes within these complexes are links between self- and object-models and RIGs (i.e., Representation Interaction Generalized), which are accompanied by convictions and a hope for wish-fulfilment. Conflictuous complexes are areas of bundled wishes, RIGs and self- and object-models with a repetitive character, thus creating areas of unbound affective information. Affects within such an area are inter-connected by k-lines, which are blocked and therefore cannot be located. In order to solve these conflictuous complexes it is necessary to retrieve this affective information into a relational reality in order to make them come alive and locatable (cf. **Figure 1**). This is attempted in dreams, their function being the search for a solution of the complex. This search

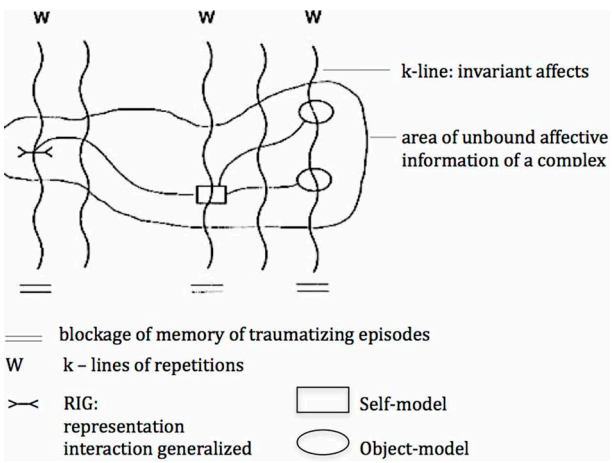


**FIGURE 1 | Memory Model of conflictuous complexes according to Moser and von Zeppelin (1996).**

[2]Ulrich Moser and Ilka von Zeppelin are fully trained psychoanalysts who have been engaged in interdisciplinary research for decades. Ulrich Moser was professor for Clinical Psychology at the University of Zurich. Since the 1960s and 70s he has been involved in modeling parts of psychoanalytic theories. By the means of computer simulation he tested the logical and terminological consistency of psychoanalytic theories of defence and the generation of dreams. Based on this basic research on dreams, he developed his own model of the generation of dreaming as well as a coding system for investigating the manifest dreams.

for a solution within a dream again is governed by the above-mentioned *security-principle* and *involvement-principle*. The following illustration may serve as an elucidation of this model.

## MEASURING THE OUTCOMES OF PSYCHOANALYTIC TREATMENT: AN INTERDISCIPLINARY CHALLENGE

Could the psychoanalytic "meaning-giving" transformation processes in the inner world of depressed patients—such as dreams—also become a part of studies based on the new possibilities of neuroimaging studies? Eric Kandel is convinced that psychoanalysis must apply these new methods in order to prove neurobiologically the sustainability of its results (Kandel, 2009 and verbal accounts) otherwise it will vanish from the world of science and only be remembered as a historical relic, a memory attesting to Sigmund Freud's enlightening spirit in the 20th century. In society it will be marginalized even though to this day it is, according to Eric Kandel, the most exciting and complex theory of the human spirit. Although many scientific theoretical and philosophical arguments could be imposed against this point of view, Kandel's assessment is surely correct in the sense that proving the sustainability of psychoanalysis and psychoanalytic therapies with neurobiological tests such as fMRI or EEGs would immediately enhance the acceptance of psychoanalytic procedures within the world of medicine.

Keeping this in mind, we perceived the opportunity of an institutional cooperation with the Max Planck Institute for Brain Research in Frankfurt, a.M. as an enormous chance to additionally examine a number of chronically depressed patients in our LAC study[3] with fMRI and EEGs (at the sleep laboratory of the SFI) which is designed as a replication of the Hanse-Neuropsychoanalysis Study (see Buchheim et al., 2012). The already tested methods of the Hanse-Neuropsychoanalysis Study are implemented here in combination with our sleep-dream-research. This is an on-going study, the so-called FRED Study (see below). Therefore, at the moment, we can only give an account of our attempts to combine *psychoanalytic* and *neuroscientific methods* within this study by presenting a single case study, which will be illustrated in the following section.

In the last sequences of this paper we also would like to illustrate our attempt to combine *clinical* and *extra-clinical (experimental) research* in the LAC depression study in another single case study. Marianne Leuzinger-Bohleber has reported the changes of dreams of a severely traumatized, chronic depressed patient as one indicator for therapeutic changes from a clinical perspective in another paper (Leuzinger-Bohleber, 2012). The same patient, part of a subsample of the 426 chronic depressed patients recruited in the LAC depression study, was willing to spend the necessary nights in the sleep laboratory of the Sigmund-Freud-Institute since investigating his severe sleeping disturbances was of clinical importance. The patient's thus elicited EEG data indeed showed pathological sleep patterns so that he had to be referred to a medical expert for sleep disturbances. As a "by-product" of this "therapeutic intervention" in the sleep laboratory, we were able to evaluate and compare his dreams obtained in the laboratory with those reported in psychoanalysis by two researchers independently. The dreams obtained in psychoanalytic treatment were analyzed and evaluated by the clinician in the psychoanalytical treatment as the analysand spontaneously reported them (see p. 19) and all dreams collected in the laboratory setting after REM awakenings were analyzed with the Moser method[4] (see p. 20) quantifying occurring changes in a standardized evaluation[5]. As laboratory dreams and home/clinical dreams are not different in a descriptive manner (length, word-count, narrativity) a comparison of both types of dreams seemed plausible. What makes them different is to whom a dream is told—a total stranger or a clinician with whom you have a close relationship. This difference shows itself with respect to dream elements told, where home dreams contain significantly more sexual and aggression/misfortune elements and laboratory dreams more bizarre elements (Foulkes, 1979; Schredl and Wittmann, 2005). The aim here was to test if changes found in clinical dreams (dream type A) with a psychoanalytic evaluation (method 1) can be found in laboratory dreams (dream type B) with the Moser method (method 2) as well, which would be indicative for a great robustness of the effect (changes in dreams).

## THE FRANKFURT fMRI/EEG DEPRESSION STUDY- FRED: APPROACHING PSYCHOANALYTIC TRANSFORMATION PROCESSES IN TRAUMATIZED, CHRONICALLY DEPRESSED PATIENTS WITH THE HELP OF IMAGING PROCEDURES[6]

FRED[7] (Frankfurt fMRI/EEG Depression Study) is an example of a fruitful combination of two domains—psychoanalysis and neurosciences. This very ambitious project currently conducted at the Sigmund-Freud-Institut (SFI) and BIC (Brain Imaging Center) in cooperation with the MPIH Frankfurt (Max-Planck-Institute for brain research)[8] seeks to examine changes of brain functions in chronic depressed patients after long-term therapies aiming to find multi-modal-neurobiological changes in the course of psychotherapies.

When looking at depression from the angle of brain-physiology, some interesting findings have been put forth: for instance that depression is related to a neurotransmitter disorder, or a frontal lobe dysfunction (cf. Caspi et al., 2003; Belmaker and Agam, 2008; Risch et al., 2009). Northoff and Hayes (2011)

[3]In the on-going large LAC depression-study we are comparing the short- and long-term effects of long-term psychoanalytic and cognitive-behavioral psychotherapies with chronic depressed patients. Up to this point we have recruited around 418 chronic depressed patients in different research centers: Frankfurt a. M., Mainz, Berlin, and Hamburg (participating research team and methods: see www.sigmund-freud-institut.de).

[4]The aim here was to test the robustness of the psychotherapeutic effect on dreams of the patient and not to compare two different methods. Therefore we did not analyse the clinical dreams with the Moser method, but chose to assess dreams of the patient in different settings by two different techniques.

[5]As chronically depressed patients in general have a poor dream recall all obtainable dreams out of REM-sleep were analyzed and are all presented here.

[6]This section is a modification of a chapter published in Fonagy et al. (2012), Fischmann et al. (2012b).

[7]Funded by the Neuro-Psychoanalysis Society—HOPE (M. Solms, J. Panksepp et al.) and the Research Advisory Board of the International Psychoanalytic Association.

[8]We are grateful to the BIC and MPIH (W. Singer, A. Stirn, M. Russ) and the Hanse-Neuro-Psychoanalysis-Study (A. Buchheim, H. Kächele, G. Roth, M. Cierpka et al.) and LAC-Depression Study for supporting us in an outstanding way.

have convincingly put forth the theory that the so-called "reward system" is disturbed in depression and that there is evidence that deep brain-stimulation can improve severe depression (also see Solms and Panksepp, 2012).

But despite all these findings, no specific brain-physiological marker for depression has yet been found. It is therefore justified to address the research question of whether changes in the course of therapy have brain-physiological correlates, which we are currently investigating in FRED.

Generally speaking, psychotherapists—especially psychoanalysts—work with what can be remembered and with recurring—usually dysfunctional—behaviors and experiences. The assumption is that this has precipitation within the brain, like synapse configuration, priming, axonal budding and more, giving ground to the hypotheses of FRED. This constitutes the neuro-psychoanalytic aspect of the FRED-study of which some preliminary results will be given in the following. Another aspect of change relevant for the study is that of clinical change found in dreams in the course of psychotherapy. The analysis of dreams with the specific method of Moser and von Zeppelin (1996)—as will be outlined—enables the comparison of empirically elicited findings with clinically reported ones from the therapist.

## METHODS

### DESIGN OF THE FRED-fMRI-STUDY

The FRED-Study investigates the hypotheses that (1) psychotherapy is a process of change in encoding conditions of memory and (2) change in memory encoding will precipitate change in brain activation patterns detectable in fMRI scanning. We hypothesized that changes in memory processing during the psychotherapy will impact the processing of trauma related memories. In the FRED study we aimed at highlighting changes in memory processing during the psychotherapy scanning depressed patients during a recognition task involving stimuli related to an underlying conflict, at the beginning of the psychotherapy and 7 and 15 months later. With such a paradigm, we predicted that the contrast [recognition of trauma-related words/sentences vs. control conditions] will highlight brain regions known to be involved in processing self-relatedness and the retrieval of autobiographical memory and/or emotional memory (emotional memory; amygdala, hippocampus, prefrontal cortex, see Buchanan, 2007; episodic memory and processing self-relatedness: medial prefrontal cortex, parietal cortex, temporal poles, see Legrand and Ruby, 2009; autobiographical memory: medial frontal cortex and hippocampus, see Maguire, 2001) and that such a pattern of activation will change across time and in the course of psychotherapy [9]. Our predictions for the session effects are as follows: Healthy control subjects without any treatment show no significant session effects, and the activation patterns remain constant over time. In successfully treated psychotherapy subjects, the patterns of activation are changing from Time 1 to Time 3, therefore producing significant session effects in statistical terms.

For this investigation, chronically depressed patients were recruited with whom an Operationalized-Psychodynamic-Diagnostics-Interview (OPD-Interview; OPD-Task-Force, 2008) concentrating on axis II (relational) and a dream-interview (see **Figure 2** below) were conducted in a first diagnostic phase. From these two interviews the stimuli for the fMRI-scanning are created individually for each patient because they are considered to be good triggers to elicit memory of an underlying conflict. Dream-Words are taken from a significant dream elicited in the dream interview and dysfunctional sentences taken from the OPD-Interview are formulated. Measurements are taken at three different time points revealing changes in activation-patterns occurring during the *course of therapy.* At T1 OPD-Sentences and Dream-Words were elicited and patients spent two nights in the sleep laboratory where verbal Dream-Reports were collected [10] in the second night after awakenings from REM2[11] to REM3[12] and in the morning. Finally the fMRI-Experiment was conducted using the OPD-Sentences and Dream-Words collected previously. At T2 and T3 EEG—Sleep Lab data and fMRI data were collected in the same manner using OPD-Sentences and Dream-Words from T1.

### PARTICIPANTS

At present 16 patients with recurrent major depressive disorders (Major Depression, Dysthymia, Double Depression for more than 24 months; Quick Inventory of Depressive Symptoms (QIDS) $> 9$ [scale range 0–27, clinical cut-off $\geq 6$]; Beck Depression Inventory (BDI) $> 17$ [scale range 0–63, clinical cut-off: $\geq 9$]; age: $M = 43$, range 23–58 years, $SD = 11.57$) take part in the FRED study. Patients of the FRED study were recruited at the Sigmund-Freud-Institut's outpatients department from the LAC-Depression Study (Leuzinger-Bohleber, 2013) conducted there, diagnosed by trained clinicians using the Structured Clinical Interviews I and II for DMS-IV Diagnosis (German version; 1998). Exclusion criteria were other psychiatric conditions as main diagnosis, substance abuse, significant medical or neurological conditions (including medical causes of depression), psychotropic medication, and eye problems. All participants were right-handed. In both groups, depression severity and general symptoms of psychopathology were assessed using the Beck Depression Inventory (BDI, Hautzinger et al., 2006[1995]) and the revised Symptom Check List (SCL-90-R, Franke and Derogatis, 2002), respectively. The control-group (13 females) consists of 18 healthy volunteers matched in age ($M = 34$, range 22–65 years, $SD = 14.59$). All participants gave written informed consent.

### STIMULI

#### *Dream—stimulus*

To gather individualized and personally relevant stimuli relating to dreams dream interviews were performed with each subject

[9] Unfortunately, this expected change may also be caused by simple forgetting and "blurring," not solely due to an effect of psychotherapeutic interventions. This is especially true for the dream-word experiment. Therefore, a control group is needed to observe the "normal" time course in non-treated subjects. Above that, the experimental procedure should take into account forgetting and blurring in the follow-up sessions by appropriate subject instructions (see below).

[10] After 10 min of REM sleep, the dreamer was awakened and asked: "Can you report a dream?"

[11] Second REM sleep period of the night.

[12] Third REM sleep period of the night.

eliciting a significant (recurrent) dream of which 30 Dream-Words were extracted together with the subject, paying close attention that they reflect the narrated dreams as concisely as possible and as close to the dream experience as possible. The dream interviews were conducted by a trained clinician (TF) and audiotaped. The participants were asked to memorize these words 1 day prior to the fMRI-investigation. These 30 Dream-Words served as stimuli during the fMRI-session (dream experiment). The control condition comprised 30 accordant words taken out of a subjectively neutral "everyday life-story," which had no specific meaning for the individual patient [13] and was taken out from a travel report in a newspaper article describing a camping vacation. They were matched in length and frequency of the words in the native language of the patient (Neutral-Words). The participant was instructed to memorize these words as well 1 day prior to fMRI-scanning. These 30 Neutral-Words served as stimuli during the fMRI-session (neutral condition). All words were presented in German.

### *OPD-stimulus*

The individualized and personally relevant stimuli relating to depressive symptoms were extracted from an OPD interview (Operationalized Psychodynamic Diagnosis; OPD-Task-Force, 2008), which were conducted with each patient. OPD is a multiaxial system assessing psychopathology focusing on pure description of symptoms (Axis V), experience of illness (Axis I), dysfunctional interpersonal relations (Axis II), psychodynamic conflicts (Axis III), and psychological structure (Axis IV) (OPD-Task-Force, 2008). The OPD interviews were conducted by trained clinicians and the dysfunctional relations blind rated independently by 2 experts. From the systematic and item-based diagnosis (OPD-Task-Force, 2008), four sentences were identified representing the core dysfunctional relationship theme of each participant (cf. **Figure 3**; condition 1).

The control condition comprised four statements of a stressful traffic situation to induce negative emotions and recall autobiographical memories with a personally relevant situation including human interactions, but without engaging in material that might interfere with participants' depression or interpersonal distress (cf. **Figure 3**; condition 2).

To allow participants to recover after emotionally demanding sentences, "relaxation" sentences were inserted between the OPD- and control condition. These sentences instructed participants to relax by thinking of a safe place. Subjects were prepared for

[13] Secured by questioning the subject prior to fMRI-assessment.

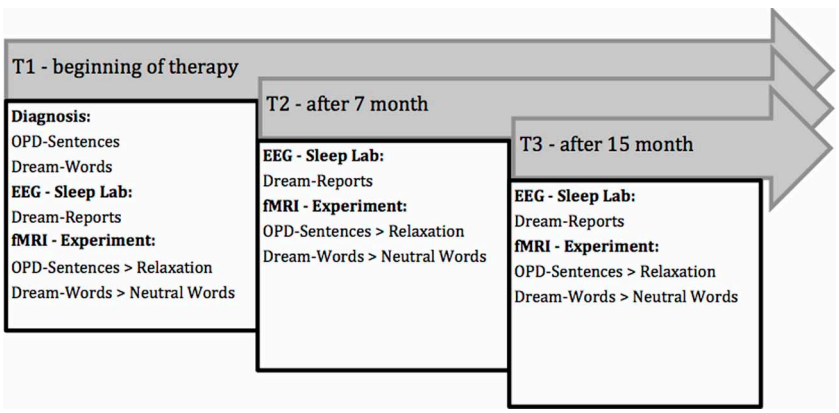


**FIGURE 2 | FRED-Design.**

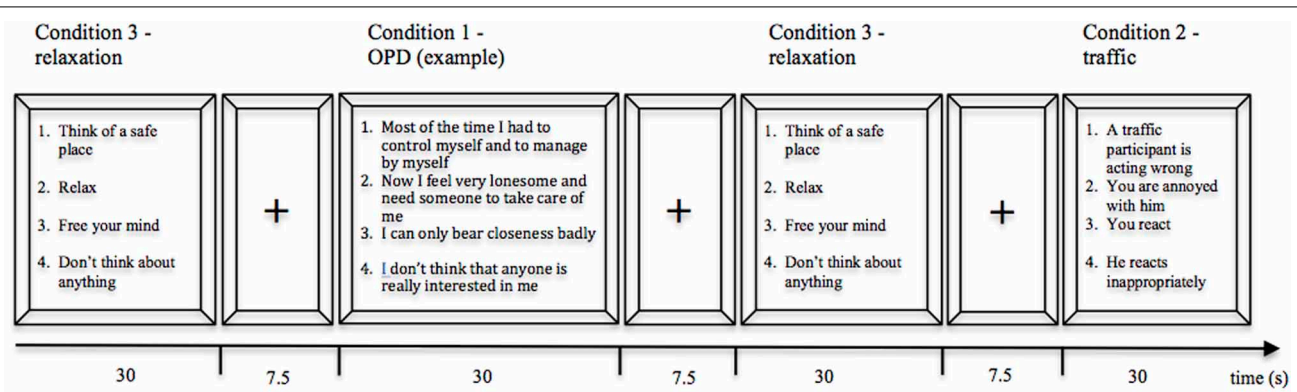


**FIGURE 3 | Block-design for OPD stimulus presentation.** Each of the 4 sentences of a condition was presented for 7.5 s in a fixed order 1–4.

the "relaxation" condition before the experiment (cf. **Figure 3**; condition 3).

Whereas the OPD sentences were derived individually for each person, "relaxation" and "control" were the same sentences across all subjects. All sentences were presented in German.

### PROCEDURE

The fMRI dream-word experiment was run as a within-subjects design with a learning/encoding phase, and a retrieval phase (during fMRI measurements). In the learning phase subjects memorized 30 Dream-Words (from his significant dream reported earlier) and 30 Neutral-Words (from a non-individual everyday life story), up to 2 days prior to fMRI scanning. At the beginning of the fMRI session and prior to scanning, subjects were presented with their individual Dream-Words as well as with their individual OPD sentences and asked whether these words adequately represented his significant dream and whether these sentences adequately represented their problematic relations. Each word series comprised 60 randomized words consisting of previously memorized 30 Dream-Words and previously memorized 30 Neutral-Words each. During recognition, subjects were presented with the 60 target words, mixed with an additional 60 Distractor-Words. The whole series of 120 items was randomized for each subject. After scanning a questionnaire assessing on a 7-point Likert scale, the extent to which the presented 120 words caused emotional arousal was given. Lying in the scanner, subjects were tested for recognition of the words learned previously. Items were presented during the recognition test for 2 s with a variable Inter-Stimulus-Interval (ISI) at a mean rate of 6.2 s randomly jumping between 2 and 8 s. Subjects had to decide on each of the 120 items, if it was old or new, by pressing one of two pre-assigned buttons with the thumb of the right hand, which was stated as being the dominant hand by all subjects. During the subsequent anatomic measurement (MPRAGE) the subjects where surveyed for their current affectivity in the scanner. Dichotomous items of the affectivity scale (Befindlichkeitsskala-Bf-S, von Zerssen, 1976, German) were presented by pairs (e.g., restful-restless) and the question asked: "Which word rather applies?" The answer was given by pressing one of two response keys (left-right). The dream experiment lasted approximately 30 min (cf. **Figure 4**).

For the OPD—experiment (block design) the four sentences of each condition (OPD, control, relaxation) were individually presented for 7.5 s while in the scanner. During the OPD block participants were asked to mentally engage in situations with significant others described by the OPD sentences and further instructed to allow spontaneous thoughts, emotions and memories to come to mind. The "control" and "relaxation" conditions also included four sentences each lasting 7.5 s. The instructions were to mentally engage either in the recalled traffic situation or to relax. The 12 "relaxation", six "control," and six "OPD" blocks were separated by a 7.5-s fixation cross. The OPD experiment lasted approximately 15 min (cf. **Figure 3**).

On retest at time points T2 and T3, the forgetting and blurring factor was considered by means of a memory refreshing procedure before scanning. Subjects were shown again the 30 dream-words as a list and asked to remember and memorize their dreams related to these words. The 30 words from the neutral story were presented as well, and the related text was read again.

### MEASUREMENT

fMRI was performed using a 3.0-Tesla head-scanner (Magnetom Allegra, Siemens, Erlangen, Germany) with a 4-channel-head coil applying an EPI mosaic sequence ($FA = 90°$, $TE = 30$ ms, matrix $64 \times 64$, interleaved acquisition, voxel size $3 \times 3 \times 3$ mm, 1.5 mm gap, 30 transverse slices covering the whole brain, $T \rightarrow C = -30°$), obtaining a series (370 measurements) of blood-oxygenation-sensitive echoplanar image volumes every 2 s.

### DATA ANALYSIS

The functional data were analyzed using the SPM 8 software from the Wellcome Department of Cognitive Neurology, London, UK, running under Matlab 12b (Mathworks Inc., Sherborn, MA). All images were realigned (for motion correction, slice timing correction), normalized into a standard space (MNI template, Montreal Neurological Institute), and smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel. For the dream-experiment a within-subject model (first level) was calculated with six conditions (Dream right and false, Neutral right and false, Distractor right and false) and three sessions (T1, T2, T3). False-conditions were variables of non-interest, contrasts Dream > Neutral (correct responses only) in T1–T3 were the effects of interest. The significance of the session-effect from T1 to T3 was estimated. The OPD-experiment was analyzed as a block-design with three conditions (OPD, Traffic, Relaxation) and three sessions (T1, T2, T3), contrast OPD > Relaxation and the session-effect T1/T2/T3 were calculated. In both experiments the head movement parameters were included as covariates of non-interest (ANCOVA without grand mean scaling).

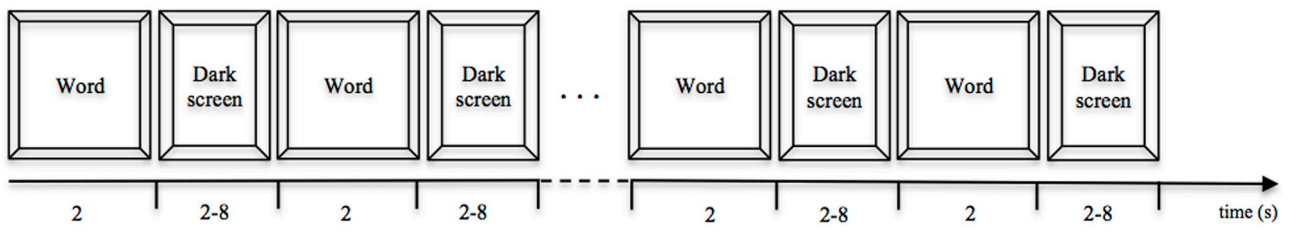


**FIGURE 4 | Event-related design for Dream stimulus presentation.** Word series of 120 words comprising 30 Dream-Words and 30 Neutral-Words previously learned +60 Distractor-Words (not learned); presented in random order with variable Inter-Stimulus-Interval (ISI) of 2–8 s (mean 6.2 s).

## RESULTS

Since the study is still on-going and reliable results of the group analysis are not yet obtained, results of a single case analysis (Mrs A., female, 50 years of age) is presented here for illustration purposes. The patient underwent a 3-year psychoanalytic treatment during which she was tested three times in the fMRI. With respect to the behavioral data, her own perception and according to the questionnaire parameters, depressive symptoms improved significantly during this period (BDI recruitment/first year/third year: 24/15/11; QIDS-C: 9/4/2).

### BEHAVIORAL DATA

Analyses of the percentage of correctly recognized target items revealed a high rate of correct responses for Dream-Words (30/30/30), Neutral-Words (28/29/29), and Distractors (58/58/59 out of 60) in the three sessions (T1/T2/T3). Mean reaction time for Dream-Words was 833 ms, for Neutral-Words 848 ms, and for Distractors 995 ms. Dream-Words produced more negative emotional arousal (T1-Rating = −3.2) than Neutral-Words (+0.2) and Distractor words (+0.1). The affectivity distinctly improved from T1 to T3 (Bf-S = 48/36/29).

### fMRI DATA

Results of the dream-experiment revealed, that Dream-Words in contrast to Neutral-Words showed a differential activation. The contrast Dream > Neutral was significant in T1 and T2, but not anymore in T3 (see **Figure 5**). The contrast showed at T1 a widespread activation pattern in left inferior frontal (area 44 and 45), left superior frontal (area 6), left intra parietal cortex (angular gyrus, middle temporal gyrus), left middle occipital gyrus, right inferior frontal gyrus pars orbitalis, right temporal pole, left precuneus, left anterior cingulate cortex, left superior medial gyrus, right inferior frontal gyrus/pars orbitalis, right middle temporal gyrus, left superior medial gyrus, left medial frontal gyrus. From T1 to T2 this distinct pattern—being significant to emotional processing of the self—largely disappears. The complete disappearance of the pattern at T3 alludes to the assumption that the dream content has lost its special importance and is now experienced in the same manner as the neutral story (cf. **Table 1**). The calculated session-effect was significant ($F = 6.8$, $p < 0.05$ FDR, corrected for multiple comparisons).

In the OPD-experiment the contrast OPD-sentences > Relaxation was significant at T1–T3 as well. The widespread activation pattern at T1 occipital (area 17 and 18), left and right hippocampus, left and right thalamus, left precuneus, left middle cingulated cortex, left inferior frontal gyrus/pars orbitalis, left precentral gyrus, vermis, left inferior frontal gyrus, right middle temporal gyrus, superior parietal lobule, cerebellum, and right and left putamen was markedly reduced at T2 and T3 (cf. **Table 2**). The calculated session-effect for this contrast was significant ($F = 10.3$, $p < 0.05$ FWE, corrected for multiple comparisons).

Both experiments distinctly showed a marked decrease of activation, lower pattern differentiation and even partial disappearance of patterns in the course of time from T1 to T3. In order to know whether or not the evolution of this pattern of activation from T1 to T3 is related to psychotherapy, it is needed to compare patients' data with control subjects' data. The data found thus far do not contradict this notion.

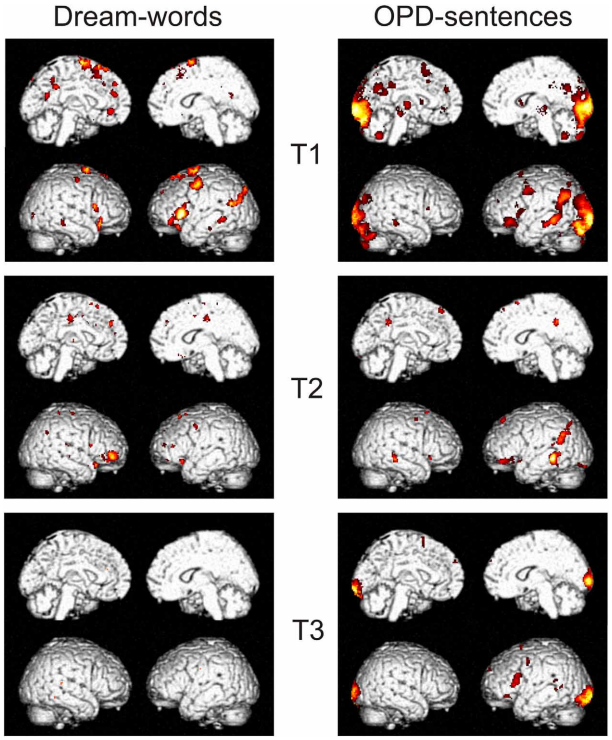


**FIGURE 5 | T-contrasts Dream words > Neutral words (left side) and OPD-sentences > Relaxation (right) of a single subject (Subject Mrs A.) over time T1–T3, all thresholds to $p < 0.05$, $T > 3.2$, 10 voxels minimum, and corrected for multiple comparisons (FDR).**

## PSYCHOANALYTIC EVALUATION OF CHANGES IN DREAMS DURING TREATMENT

Within the FRED-study, dreams were not only studied from a neurophysiological perspective but also from a psychoanalytic standpoint by analysing the manifest dream using the Moser method. This method is based on the analysis of dreams under problem-solving aspects, which strongly relies on affect-regulation, since the success or failure to resolve a conflictuous complex, assumed to be underlying the dream, will ultimately be determined by it (see below). Analysis is done by scrutinizing the manifest dreams for certain aspects, among others: elements positioned within the dream-world, observable interactions taking place between self and others or the absence of them and interruption of dream-scenes, which allude to affective overflow rendering such interrupts necessary. The following describes the dream coding system of Moser and von Zeppelin as it has been applied here.

## THE DREAM CODING SYSTEM OF MOSER AND VON ZEPPELIN

Based on their model of cognitive-affect regulation, Moser and von Zeppelin (1996) have developed a coding system which can be used to analyse dream material. It is an evaluation

**Table 1 | Contrast Dream-Words > Neutral-Words at time point T1.**

| Anatomical region | Hemisphere | BA | MNI | | | Voxel | *T* |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Infer frontal gyrus | Left | 44/45/3b | −48 | 18 | 4 | 833 | 6.7 |
| Superior frontal gyrus | Left | 6 | −16 | −2 | 72 | 683 | 6.0 |
| Postcentral gyrus | Left | 6 | −50 | −8 | 52 | 397 | 6.1 |
| Intraparietal cortex (PGp, PGa, PFm) | Left | 39/40 | −46 | −74 | 26 | 370 | 4.5 |
| Superior frontal gyrus | Right | 6 | 14 | 4 | 74 | 171 | 6.5 |
| Inferior frontal gyrus (orbital) | Right | 45 | 48 | 26 | −8 | 131 | 4.6 |
| Anterior cingulate cortex | Left | 32 | −12 | 42 | −4 | 89 | 5.0 |
| Middle temporal gyrus | Left | 35/36 | −54 | −44 | −4 | 88 | 4.6 |
| Superior medial gyrus | Left | 32 | −10 | 48 | 20 | 80 | 4.0 |
| Inferior frontal gyrus (orbital) | Right | 45 | 34 | 22 | −14 | 71 | 3.8 |
| Middle temporal gyrus | Right | 22 | 50 | −34 | −8 | 49 | 4.1 |
| Precentral gyrus | Right | 6 | 54 | −12 | 60 | 44 | 4.6 |
| Superior medial gyrus | Left | 32 | −6 | 48 | 38 | 44 | 3.2 |
| Middle frontal gyrus | Left | 8 | −28 | 16 | 64 | 40 | 3.8 |

*All clusters significant after correction for multiple comparisons (FDR, $p < 0.05$).*

*MNI xyz, local maxima coordinates (Montreal Neurological Institute), T-test statistics, BA-Brodmann area.*

**Table 2 | Contrast OPD-sentences > Relaxation at time point T1.**

| Anatomical region | Hemisphere | MNI | | | Voxel | *T* |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| 1. Occipital lobe/Cerebellum/Lingual gyrus/Fusiform gyrus | Left/Right | (Multiple clusters) | | | 12,590 | >2.7 |
| 2. Thalamus/Hippocampus: | Left | | | | 464 | >2.7 |
| Thalamus | Left | −12 | −14 | 6 | | 3.6 |
| | | −14 | −16 | 4 | | 3.5 |
| Hippocampus | Left | −24 | −26 | −10 | | 4.4 |
| 3. Precuneus/Cingulate: | Left | | | | 421 | >2.7 |
| Precuneus | Left | 0 | −62 | 34 | | 3.5 |
| | | −4 | −56 | 22 | | 3.0 |
| Middle cingulate | Left | −4 | −38 | 36 | | 3.2 |
| | | −8 | −42 | 38 | | 3.1 |
| 4. Inferior frontal gyrus | Left | | | | 339 | >2.7 |
| | | −50 | 34 | −12 | | 3.4 |
| | | −38 | 32 | −4 | | 3.8 |
| | | −46 | 24 | −10 | | 3.6 |
| 5. Hippocampus/Thalamus | Right | | | | 295 | >2.7 |
| Thalamus | Right | 26 | −26 | −4 | | 4.8 |
| Hippocampus | Right | 28 | −22 | −16 | | 4.4 |
| | | 28 | −22 | −16 | | 2.9 |
| 6. Precentral gyrus | Left | | | | 273 | >2.7 |
| | | −46 | 2 | 40 | | 4.1 |
| | | −50 | 0 | 48 | | 3.3 |
| | | −36 | −2 | 46 | | 3.0 |
| 7. Inferior frontal gyrus | Left | −44 | 10 | 10 | 98 | 3.3 |
| 8. Middle temproal gyrus | Right | 58 | −32 | −10 | 67 | 3.5 |
| 9. Superior parietal gyrus | Left | −26 | −66 | 54 | 50 | 3.2 |
| 10. Superior frontal gyrus | Left | −12 | 46 | 30 | 48 | 3.3 |
| 11. Putamen | Right | 20 | 10 | 6 | 39 | 3.3 |
| 12. Putamen | Left | −20 | 18 | 44 | 32 | 3.2 |

*All clusters significant after correction for multiple comparisons (FDR, $p < 0.05$).*

*MNI xyz, local maxima coordinates (Montreal Neurological Institute), T-test statistics.*

| Sit. | PF (Positioning Field) | LTM (Loco Time Motion) | IAF (Interaction Field) |
|---|---|---|---|
| S1 | SP<br>PLACE (dam)<br>$CEU_1$ (bridge)<br>$CEU_2$ (mountains)<br>ATTR (steep) | | |
| S2 | SP<br>PLACE (slope)<br>$CEU_3$ (house) | LTM $CEU_2$<br>1 ATTR | |
| /C.P./ | | | |
| S3 | SP<br>$CEU_3$<br>ATTR (rapidly sliding) | | IR.C |
| /C.P./ | | | |
| S4 | SP<br>$CEU_1$ | | IR.S |

**FIGURE 6 | Moser and von Zeppelin dream coding sheet.** SNbr, Situation (dream-scene); /C.P./, cognitive process (Interrupt); SP, self processor (dreamer); CEU, cognitive element inanimate; ATTR, attribute; IR.C, interactive relation connecting; IR.S, interactive relation self-changing.

system with formal criteria to investigate manifest dream-content and its changing structures (for a more detailed description cf. Fischmann et al., 2012a).

According to Moser and von Zeppelin the regulating processes of dream-organization as described in our introductory remarks can be detected by:

- how elements are positioned in the dream-world (i.e., potentiality for involvement)
- monitoring the dream activity (preparing or omitting involvement),
- allocating affective feedback information of each dream-situation and its consequences,
- allocating regulating procedures responsible for changes (interaction).

The coding system defines formal criteria and structures of a dream discernable within the manifest dream narrative elucidating affect-regulation processes of the dream (see **Figure 6**): number of situations, type of places and social settings named in a dream (descriptions, attributes), objects occurring (descriptions, attributes), placement, movement, interactions of objects as well as the question of whether the dreamer himself was involved in interactions, or if he remains a spectator.

As mentioned above two principles of affect-regulation are assumed: (A) the security-principle and (B) the involvement-principle, which can be discriminated by the "positioning" of elements within the dream and through "interaction." Common to both principles is their ruling by negative and positive affects, i.e., anxiety is the motor for an enlargement of security also regulating involvement by, for instance, breaking off interaction and generating a new situation. It is assumed that problem solving can only take place and be tested in interaction; therefore the dream tends toward interaction.

It is assumed that the more elements used in a dream scene, the more possibilities are available for the dreamer to regulate his affects and contents processed in the dream. If the dream omits "interaction," security aspects are dominant.

The following clinical case focuses on the analyses of two distinct dream series from the first 3 years of therapy. For one a dream series enfolding two dreams taken from clinical sessions of the psychoanalytic treatment (clinical dreams)[14] is compared to a dream series comprising four dreams, which were elicited in the dream laboratory (laboratory dreams). This comparison highlights how clinical and experimental data combined give mutually enriching insights into changes occurring during the course of treatment.

## CLINICAL CASE: ANALYSIS OF A DREAM SERIES IN THE COURSE OF THERAPY

### BIOGRAPHY AND TRAUMA HISTORY

Marianne Leuzinger-Bohleber has described the clinical and biographical background of this severely traumatized, chronic depressed patient extensively in another paper (Leuzinger-Bohleber, 2012). There she illustrated from her clinical perspective how the manifest dreams as well as the dream work changed during psychoanalysis and also reported on the transformation of the inner (traumatic) object world. In this paper we would like to contrast her clinical views with a more systematic investigation of the changes in the manifest dreams.

Here a short summary of the clinical material:

The patient explained in the assessment interviews that he had been suffering from severe depression for the last 25 years, and that he came to our Institute because after the last depressive breakdown he had submitted an application for a retirement pension. The doctor who assessed his application concluded that he did not require a pension, but an "intelligent psychoanalysis,"—initially a response Mr W. found highly insulting. He felt that he had not been taken seriously, especially his substantial physical symptoms; the unbearable pains involving his entire body, his acute eating disorders as well as his suicidal tendencies. Furthermore, the patient suffered under severe sleeping disorders. Often he is unable to sleep at all. As a rule, he wakes up after one and a half hours, or after 3 h at the most. He feels physically exhausted and is barely able to concentrate on anything.

Mr W. had already undergone several unsuccessful attempts at therapy, including behavioral therapy, Gestalt Therapy, "body therapy" as well as several inpatient treatments in psychiatric and psychosomatic clinics. He is among the group of patients that for the most part seem unable to respond to psychotropic drugs, and whose relapses occur at ever-shorter intervals and with increasing intensity. After many consultations with various psychiatrists and neurologists, he then discovered that solely Lyrica[15] enabled him more or less to deal with his states of physical stress and his anxiety attacks.

The patient is an only child. One of the known details about his early history is that he was a "cry-baby." When he was 4

[14]The clinical dreams are analyzed by a clinician (M. Leuzinger-Bohleber) using a specific technique largely based on an earlier version of Moser's memory- and affect-regulation-models is applied to the manifest content of the clinical dreams (cf. Leuzinger-Bohleber, 1987, 1989, 2012, p. 324), whereas the laboratory dreams are analyzed by the Moser coding method as outlined above.

[15]Lyrica (generic name: Pregabalin) is an anticonvulsant drug used for neurotic pain, also effective for generalized anxiety disorder (since 2007 approved for this use in the European Union).

years old Mr W.'s mother fell seriously ill. W. was admitted to a convalescent home for children, evidently founded on authoritarian, inhumane educational principles reminiscent of National Socialist ethos. Just how traumatic an experience this stay in a home was, is something that became apparent during psychoanalysis. Mr W.'s first childhood memories revolve around the following event: he recalls how his father took him by the hand and led him out of the home. He also recalls how a girl had been forced to eat her own vomit.

Mr W. experienced two further separations from his ill mother, but these incidents had proven less traumatic since he had been taken in by relatives.

In spite of the dissociative states following the traumatic separations and his social isolation, W. was a good pupil, who went on to complete his first apprenticeship training and later his university studies. During adolescence, he had a psychosomatic breakdown, which the parents diagnosed as a "growing up crisis." At the age of 15 years, he met his first girlfriend. His condition improved. At the age of 22 he ended the relationship with his first girlfriend because he fell in love with another woman. Although the separation ran in his favor, he reacted very severely to it. Although he had also initiated the separation from his second girlfriend, he suffered for weeks due to the separation. After entering another relationship he was dramatically overcome by a nervous breakdown during a party held by his new girlfriend: he had to be taken to hospital due to hyper-ventilation (panic attacks).

As already mentioned, Mr W. had undergone several psychotherapies. Although all his therapies alleviated his problems, "none of them cured him." His depressions became worse and worse until they became chronic.

During the current treatment his self-reported depressive symptomatology improved over the first 2 years of treatment considered here (BDI recruitment/first year/ beginning of the third year: 48/40/30), whereas external assessment of depressive symptomatology by a trained clinician in the LIFE interview remained salient (QIDS-C: 15/16/17). It is interesting that the beginning transformation of the inner world of the patient became observable in the changes of the manifest dreams (see below), but, after the first 2 years of treatment, had not been seen yet by the independent clinician in the LIFE interviews.

## DREAM SERIES ELICITED IN THE PSYCHOANALYTIC TREATMENT

Within the framework of this paper we cannot elaborate on the psychoanalytic understanding of the transformations of the manifest dreams or on the work with the dream associations in the psychoanalytic sessions (see e.g., Leuzinger-Bohleber, 2012, 2013). We can only communicate a first impression of these changes in two dreams, one from the end of the first and one from the third year of treatment. The first dream reported here is a typical dream of a severely traumatized person where the patient himself is in a position of an observer: the dream subject is in an extreme, life threatening situation, completely helpless, in unbearable pain—and not being helped by anyone. In the second dream the patient is the active dreamer, observing a situation which still is painful but with hope that "something can be done" in order to overcome a hopeless situation

### CLINICAL DREAM 1: FIRST YEAR OF TREATMENT

> "I catch sight of a man lying at the side of the road severely wounded—his intestines are spewing out, and everything is saturated in blood…A helicopter appears. It is unclear as to whether the man is still being shot at, or whether one should go to his aid. Someone appears claiming that the man now has passed away. I notice that the man is still alive and he really does open his eyes and enquires: why is nobody helping me? The woman hands him a lid of a saucepan, which he should hold over his open wound …I then wake up, riveted by panic…" (Leuzinger-Bohleber, 2012, p. 66/67)

### CLINICAL DREAM 2: BEGINNING OF THIRD YEAR OF TREATMENT

> "I am gazing at a group of people all smeared with clay who are working together on the outer shell of a house. A cold wind blows—the work is torturous, arduous, and barely tolerable. And yet, in the dream I have a certain sense that the men will succeed: at some point the house will be built and provide them with a warm home. I then turn to my wife and say: "You see, we can do it –one just has to stay together…" (Leuzinger-Bohleber, 2012, p. 70/71)

By comparing the clinical dream from the beginning of psychoanalysis with the one of the beginning of the third year of analysis, Leuzinger-Bohleber observed changes in the patterns of the relationships, where *the dream-subject shows better relationships with others* (e.g., people helping each other in the second reported dream). In the first dream the dream subject had mostly been alone: no one helped him and soothed his anxieties, panic and despair. *The range of actions of the dream-subject is increased* and *the emotional spectrum is enlarged* (in the dreams at the beginning of psychoanalysis we find only panic—at the beginning of the third year of analysis we also observe surprise, joy, satisfaction, humor and yet continuous anxieties and pain).

There is also a noted change in the dream atmosphere, with the variety of affects as well as its increased intensities and manifest anxiety being less frequent. The dreamer's increased capability to perceive different and even contradictory emotions become more and more visible. New feelings of anger, rage but also positive affections, tenderness and sexual attractions appear in the dreams toward the second year of treatment. The dream subject is no longer a (distant) observer but plays an active part and is involved in intensive emotional interaction with others.

Furthermore, Leuzinger-Bohleber distinguished *clearer problem-solving strategies* (more successful than non-successful problem-solving) and a *broader range of different problem-solving strategies* from the manifest dreams. The dream-subject is no longer as flooded as in a traumatic situation in which he experiences extreme helplessness and lack of power. In his dreams around the beginning of the third year of psychoanalysis he encounters objects willing to help and support him. This seems to be a very important indicator that the inner object world of the severely traumatized patient has changed (see introduction and Leuzinger-Bohleber, 2012, 2013).

## DREAM SERIES ELICITED IN THE DREAM LABORATORY

In the following a total of four dreams—two from the end of the first year of therapy and two from the end of the second year all

elicited in the dream laboratory—will be analyzed for changes within the course of therapy using the Moser method.

#### LABORATORY DREAM 1—END OF FIRST YEAR OF TREATMENT

> "I am standing on a bridge over a dam. To my right and left are steep slopes—mountains (S1). There is a landslide. I see the slope and an entire house approaching me very fast, rapidly sliding rushing toward me (S2). I think to myself, that I will not be able to escape it (/C.P./). I am running (S3) and am amazed at how fast I can run (/C.P./). I succeed in saving myself from the rapidly approaching house (S3). I am in safety at the edge of this bridge (S4)."

In order to analyse this dream with the Moser method each and every element of a situation is given a code (cf. **Figure 3**) in the respective column of either the positioning field (PF), the field of trajectories (LTM) or the interaction field (IAF):

From here the dream can be analyzed as follows: the first situation of this dream (S1) is coined by the security principle—many cognitive elements are simply being placed. But it also hosts a multitude of involvement potential as many attributes are being named for the elements placed. In the second situation (S2) a first attempt is made to deal with this potential—albeit rather limited (LTM)—but again increasing potentiality by adding another attribute (ATTR). As a result the affectivity seems to increase to such an extent that the dream-scene has to be interrupted by a comment (/C.P./). In S3 the dreamer finally succeeds to invoke a "*successful*" interaction between the threatening cognitive element [$CEU_3$ (house)] and himself (SP). Initially this leads to another interrupt: the dreamer is surprised by his capabilities and finally in S4 a cathartic self-changing interaction is conjured up: he is in safety.

In summary the patient describes a threatening situation, which is initially determined by the security-principle. The relatively sophisticated description of the first scene bears potential, which the dreamer makes full use of in order to regulate the threatening affects. The wish to "bring himself to safety" is fulfilled in this dream.

#### LABORATORY DREAM 2—END OF FIRST YEAR OF TREATMENT

> "There are more people in the room. I wear this cap. You three are here and somebody else, who will come up right after me. He makes a lot of pretensions. It is morning and I wake up. I wear this cap and am hooked up to all those cables (S1). It is lively around me and you and the others are walking around, talking to each other. I pick up on you whispering and being annoyed at someone or making fun of him. The one that you are annoyed with is in the room as well, and he is supposed to put the cap on after me (S2). I remember that I have seen him once before in front of the door of my analyst (S3). He is here in the room and constantly makes pretensions. Everything should be the way he wants it. You are annoyed that you have to fulfill these wishes (S4). I think to myself: "Just take it easy" (/C.P./)."

Obviously this is a "laboratory dream." The patient uses the research situation as an opportunity to regulate his anxieties of being "too pretentious." He projects this onto an object processor (OP) turning into an observer. Thus, he successfully distances himself, which gives him the possibility to comprehend the events in more detail.

In the 1st situation (S1) there is a lot of potential to regulate affects—albeit still governed by the security principle. It includes a social setting (SOC SET), variable attributes (ATTR) and a lot of processors inviting action. By placing another patient ($OP_2$) into the dream scene the dreamer (subject processor SP) gets the opportunity to take an observational stance, which leads to a movement (trajectory LTM) of the $OP_1$ group of researchers in S2. S3 is regulated by the security principle and the potential existent in S2 (LTM) cannot be exploited in S3. In S4 finally this is achieved by an interaction just to disembogue in another interrupt. The affectivity of the situation increases to such an extent that it has to be interrupted: the dreamer cautions the object processor ($OP_2$) or rather himself "to take it easy."

#### LABORATORY DREAM 3—END OF SECOND YEAR OF TREATMENT

> "A Formula-1 race with Michael Schumacher (S1). Directly after the race he flies to Germany, in order to inaugurate a bridge (S2). Totally bonkers (/C.P./). He is in Germany and inaugurates the bridge (S3). He speaks with a few people sitting at a table. I am sitting at the table next to it and observe him and the others in debate (S4). How do I come up with something like this? (/C.P./)"

Again the dreamer takes an observational stance. In contrast to the previous dream he succeeds in creating a connecting interaction between two CEs, which is not interrupted but seamlessly leads into a displacement relation. Although this may still be considered to be a distancing manoeuvre from an affective event, it is not as marked as in the previous dream. The involvement principle is more distinct here than it had been previously. The interrupt at the end of the dream is not a rebuke as before, but rather expresses astonishment at what occupies his mind and a (conscious) approximation to the underlying complex may be assumed.

#### LABORATORY DREAM 4—END OF SECOND YEAR OF TREATMENT

> "I am on my way with my little son. Other children and adults are with us. A boy is there too, who has something against my son. It is summer. It is warm. We are walking along the banks of a river (S1). We want to buy a wagon or trailer (S2). The children are of different ages. One boy is already 11 or 12 years old. This boy is on edge, because the other children and also my son are so young and they cannot do what he wants them to do, because they are too small (S3). Then my mother appears. She sews a button back onto my shirt (S4). I don't know how this fits in (/C.P./). I say: "Just leave this stupid button alone." This unnerves me (S5). I am there to oversee everything. A woman is there too. She is the mother of that boy (S1).

This dream is regulated from the beginning by the involvement principle, which alludes to an advanced therapeutic effect. In all successive situations more interactions appear: also connecting

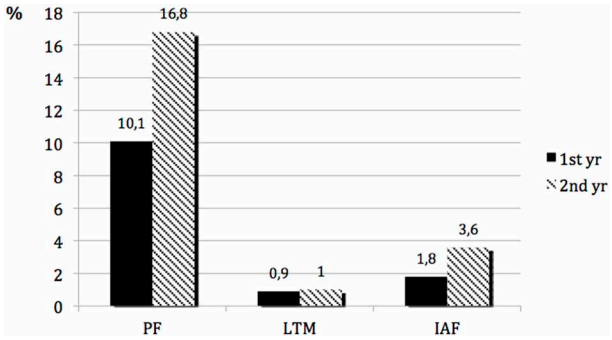


**FIGURE 7 | Relative frequency of single codes relativized by the average number of words.**

self-changing relations of subjects and objects. The self-processor (SP) himself is involved and does not have to retreat into an observing position anymore (no IR.D)—he faces his affects increasingly. After S4 triggers an interrupt, the dreamer (SP) interactively "fends this off" via verbal relation (V.R.). Thus, we might assume that the dreamer progressively deals with the affects underlying the dream-complex in an interactive manner and is able to depict them in dream scenes. The affects are no longer isolated—which implies that previously isolated affects of the dream-complex can be integrated now.

In summary, the analysis shows that the patient's laboratory dreams from the end of his first year in therapy were abundant with anxieties and yearning for security making him hesitant to get involved with others. But even in these dreams he already showed potential of what we might consider to be the result of the on-going therapy, i.e., signs of involvement abilities, enabling him to make use of others by projecting his fears into them and *testing* if he could bear the rising anxieties involved in the actions he projected onto them while he still remained in a distant observer position. But at this stage of therapy his fears of getting involved got the better of him and he could not yet exploit these potentials. At the end of the second year of analysis his dreams reveal his enhanced abilities to get involved (dream 4 is largely dominated by the involvement principle from the beginning) being abundant with interactions with others portraying his increased ability to face his affects. Albeit rising affectivity is still met with an *interrupt* it is now followed by a dream scene of a different quality: he can fend off his rising anxiety via an *aggressive* response (V.R. S5 in dream 4) heralding a progressive approach to the underlying (unconscious) conflict-laden dream-complex by integrating affects into existing memory networks.

To illustrate these changes occurring from a more experimental perspective the following graph might be helpful (see **Figure 7**):

There is a clearly recognizable increase in potentials (PF) from the end of the first year to the end of the second year dreams that can be exploited for interaction (IAF). The finding of an enhanced ability to get involved can be seen here by simply having a look at the manifest dreams.

## CONCLUDING REMARKS

This extra-clinical analysis of the manifest dream-content of the patient's laboratory dreams substantiate his clinical improvement as Leuzinger-Bohleber illustrated in her analysis of the transformations of the manifest content of the clinical dreams (see Leuzinger-Bohleber, 2012).

The consistencies of the clinical and extra-clinical analyses are remarkable, which from a scientific perspective is of utmost relevance. But to be sure, the clinical case study still provides greater psychodynamically relevant clinical and structural information, as the extra-clinical analysis suffices with the content of the manifest dreams and has no further biographical data at hand with which results could be enhanced. The consistency in the finding on the other hand consolidates the reliability of the clinical case analysis.

Combining clinical and extra-clinical research remains a great challenge particularly in psychoanalytic psychotherapy research. It is still a strength of clinical research in psychoanalysis to communicate the unique and complex insights gained in intensive psychoanalyses by narratives because many a "truth can only be told and not be measured." At the same time psychoanalysis, as all "contemporary psychotherapies," is obliged to show the short-term and long-term effects of their treatments to the psychoanalytic as well as to the non-psychoanalytic community. The latter often requires the consideration of criteria of the so-called evidence based medicine in such effectiveness studies (see political context of the LAC depression study, www.sigmund-freud-institut.de). An alternative, innovative approach to "prove" therapeutic changes in an "objective way" is to investigate patients during their psychoanalyses by instruments like the EEG and the fMRI (if the patients are willing to undergo these procedures).

The changes found in the dream material (clinical and laboratory) of the patient presented here could not be tested neurophysiologically as Mr W. had to be excluded from fMRI because of a physical exclusion criterion (heart operation). Therefore, we exemplified clinical changes that have a specific neurobiological resonance by another case of the FRED study that of Mrs A. Data of change using the dream experiment in this single case revealed in the course of therapy the recognition or rather re-sounding of initially significant dream content at the beginning of therapy specifically activated fronto-medial areas, the Precuneus and the Left Parietal Lobe, which did not substantiate after 1 year of therapy. The disappearance of these areas—being significant to emotional processing of the self—at T3 allude to the assumption that the dream content has lost its special importance and is now experienced in the same manner as the neutral story. These changes in and de-differentiation of activation patterns coincided with clinically found improvement. Whether this is indeed related to psychotherapy needs to be analyzed by a group comparison of patients' data with control subjects' data. This will be the subject of upcoming papers.

In this paper we hope to have illustrated the fascinating similarities between the clinical use of dreams as an indicator for changes in the inner (traumatic) object world in psychoanalyses

and the systematic, "scientific" investigation of laboratory dreams by the so-called "Moser-method." We also could show that such changes are also evident on a neurobiological level. The clinical case report focused on the importance of the psychoanalytic context of dreams, the observation of transference and countertransference reactions, the associations of the patient and the analysand etc. necessary to unravel the unconscious meaning of the dream and thus trying to contribute to the "meaning-finding process" of this severely traumatized patient (Leuzinger-Bohleber, 2012). One great advantage of the psychoanalytic clinical "research" on dreams continues to be the understanding of the meaning of a dream in cooperation with the dreamer, that is the patient. His association, and conscious and unconscious reactions to a dream interpretation still are the criteria in order to evaluate the "truth" of an interpretation (see. e. g. Leuzinger-Bohleber, 1987, 1989, 2008). To make a long story short: the transformation of the unconscious world (like dreams)—and as products of it, the maladaptive emotions, cognitions and behaviors ("symptoms") of the patient—still remain the final psychoanalytic criteria for a therapeutic "success" based on "true insights" of the patient in his unconscious functioning.

On the other hand this kind of "truth" often remains fuzzy and subjective at least in the eyes of the non-psychoanalytic scientific community. Therefore, we have seized the unique opportunity to analyse changes in the manifest dreams by a theory-driven, precise systematic coding system on the one hand and neurobiological evidence on the other hand. These analyses have a high reliability—and inter-subjectivity—and thus may convince independent observers or even critics. Thus, we hope to have illustrated in this paper that the results of clinical research within the frame of intensive psychoanalytical treatments might be combined with extra-clinical research thus emphasizing their empirical, clinical and neurobiological value for future research.

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# The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs

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Entropy is a dimensionless quantity that is used for measuring uncertainty about the state of a system but it can also imply physical qualities, where high entropy is synonymous with high disorder. Entropy is applied here in the context of states of consciousness and their associated neurodynamics, with a particular focus on the psychedelic state. The psychedelic state is considered an exemplar of a primitive or primary state of consciousness that preceded the development of modern, adult, human, normal waking consciousness. Based on neuroimaging data with psilocybin, a classic psychedelic drug, it is argued that the defining feature of "primary states" is elevated entropy in certain aspects of brain function, such as the repertoire of functional connectivity motifs that form and fragment across time. Indeed, since there is a greater repertoire of connectivity motifs in the psychedelic state than in normal waking consciousness, this implies that primary states may exhibit "criticality," i.e., the property of being poised at a "critical" point in a transition zone between order and disorder where certain phenomena such as power-law scaling appear. Moreover, if primary states are critical, then this suggests that entropy is suppressed in normal waking consciousness, meaning that the brain operates just below criticality. It is argued that this entropy suppression furnishes normal waking consciousness with a constrained quality and associated metacognitive functions, including reality-testing and self-awareness. It is also proposed that entry into primary states depends on a collapse of the normally highly organized activity within the default-mode network (DMN) and a decoupling between the DMN and the medial temporal lobes (which are normally significantly coupled). These hypotheses can be tested by examining brain activity and associated cognition in other candidate primary states such as rapid eye movement (REM) sleep and early psychosis and comparing these with non-primary states such as normal waking consciousness and the anaesthetized state.

**Keywords: serotonin, default mode network, criticality, entropy, 5-HT2A receptor, metastability, consciousness, REM sleep**

## INTRODUCTION

The main aim of this paper is to introduce a new theory of conscious states that incorporates principles of physics, neurobiology, and psychoanalysis. The theory is intended to assist our understanding of the makeup of the human mind, addressing such questions as: "how does the normal waking consciousness of healthy adult humans relate to other states of consciousness?" "how does the human brain maintain its normal state of waking consciousness?" and "what happens to the human brain's functionality when non-ordinary states such as rapid eye movement (REM) sleep/dreaming, early psychosis and the psychedelic state occur?"

At its core, the entropic brain hypothesis proposes that the quality of any conscious state depends on the system's entropy[1] measured via key parameters of brain function. Entropy is a powerful explanatory tool for cognitive neuroscience since it provides a quantitative index of a dynamic system's randomness or disorder while simultaneously describing its informational character, i.e., our uncertainty about the system's state if we were to sample it at any given time-point. When applied in the context of the brain, this allows us to make a translation between mechanistic and qualitative properties. Thus, according to this principle,

[1]Entropy in its purest information theoretical sense is a dimensionless quantity that is used for measuring uncertainty or ignorance about the state of a system. By implication, entropy/uncertainty is greater the more random a system is. Thus, entropy is most strictly a measure of uncertainty but it also reflects the degree of randomness or disorder in a system (Ben-Naim, 2012).

increased subjective uncertainty or "puzzlement" accompanies states of increased system entropy. These ideas are consistent with Karl Friston's free-energy principle[2] and readers interested in Bayesian inference and the mechanisms by which the brain is hypothesized to minimize free-energy/surprise should consult this work (Friston, 2010).

System entropy, as it is applied to the brain, is related to another current hot-topic in cognitive neuroscience, namely "self-organized criticality"[3] (Chialvo et al., 2007). The phenomenon of self-organized criticality refers to how a complex system (i.e., a system with many constituting units that displays emergent properties at the global-level beyond those implicated by its individual units) forced away from equilibrium by a regular input of energy, begins to exhibit interesting properties once it reaches a critical point in a relatively narrow transition zone between the two extremes of system order and chaos. Three properties displayed by critical systems that are especially relevant to the present paper are: (1) a maximum number of "metastable" or transiently-stable states (Tognoli and Kelso, 2014), (2) maximum sensitivity to perturbation, and (3) a propensity for cascade-like processes that propagate throughout the system, referred to as "avalanches" (Beggs and Plenz, 2003). There is growing evidence that brain activity, like much of nature, displays critical behavior (Beggs and Plenz, 2003)—and this raises some interesting questions: e.g., does the brain activity of healthy-adult-humans exhibit characteristics of criticality during normal waking consciousness, or are there other states of consciousness in which these characteristics are even more pronounced?

Another major topic that is covered in this paper is the psychoanalytic model of the structure of the mind (i.e., Freud's "metapsychology"). Specifically, we discuss some of the most fundamental concepts of Freudian metapsychology, with a special focus on the ego[4]. We focus on the ego because it is one of Freud's less abstract constructs and it is hypothesized that its disintegration is necessary for the occurrence of primary states. The ego can be defined as a sensation of possessing an immutable identity or personality; most simply, the ego is our "sense of self." Importantly however, in Freudian metapsychology, the ego is not just a (high-level) sensation of self-hood; it is a fundamental system that works in competition and cooperation with other processes in the mind to determine the quality of consciousness. It is because Freud described "the ego" in this mechanistic sense that it can be considered a useful complement to the more widely used concept of "the self." Effectively, the terms "ego" and "self" are synonyms, except that "the ego" has a background in Freudian metapsychology.

Finally, the shared topic that connects all of the above and offers a unique potential for their empirical study is the psychedelic drug state. In the following section we make the case that scientific research with psychedelics has considerable potential for developing aspects of psychoanalytic theory and for studying human consciousness more generally. Citing recent neuroimaging findings involving the classic psychedelic drug, psilocybin, the psychedelic state is described as a prototypical high-entropy state of consciousness (i.e., higher than normal waking consciousness). Intriguingly, we show evidence that the brain exhibits more characteristics of criticality in the psychedelic state than are apparent during normal waking consciousness. Moreover, this leads to the proposal that the brain of modern adult humans differs from that of its *closest* evolutionary and developmental antecedents because of an extended capacity for entropy suppression, implying that the system (i.e., the brain) gravitates away from criticality proper toward a state of slight sub-criticality. The psychological counterpart of this process is the development of a mature ego[5] and associated metacognitive functions (see below for relevant definitions of these terms). Specifically, we propose that within-default-mode network (DMN)[6] resting-state functional connectivity (RSFC)[7] and spontaneous, synchronous oscillatory activity in the posterior cingulate cortex (PCC), particularly in the alpha (8–13 Hz) frequency band, can be treated as neural correlates of "ego integrity." Evidence supporting these hypotheses is discussed in the forthcoming sections.

Before beginning it is important to address an initial point of potential ambiguity. The view taken here is that the human brain exhibits greater entropy than other members of the animal kingdom, which is equivalent to saying that the human mind possesses a greater repertoire of potential mental states than lower animals (see Giulio Tononi's information integration theory of consciousness cited below). Thus, if referring to human evolution beyond our closest *surviving* relatives then it would be misleading to suggest that entropy-suppression is the defining property of the human brain—indeed, it might be more accurate to speak of entropy-expansion. The evolution of human consciousness may have occurred through a process of relatively rapid

[2]The free energy principle is an extension of predictive coding (Dayan et al., 1995) and tries to explain how biological systems, such as the brain, maintain their order by developing inferences and behaviors that serve to minimize surprise and uncertainty. Free-energy is formally related to entropy in the information theoretical sense, where entropy (uncertainty) is the average of free-energy (surprise) (Friston, 2010). See also (Friston et al., 2012a) for a philosophical discussion of free-energy.

[3]Self-organized criticality (SOC) is a property of certain systems that gravitate toward a 'critical' point in a transition zone between order and disorder. Critical systems display certain characteristics such as power-law scaling (Bak et al., 1987). SOC is typically observed in slowly driven non-equilibrium systems, with many units that interact in a non-linear fashion (Bak et al., 1987; Jensen, 1998).

[4]The ego can be defined as a sensation of possessing an integrated and immutable identity, i.e., "this is me" or "I am like this." It is equivalent therefore with one's sense of self. In psychoanalytical theory however, the ego is also a system which works in concert with and against other processes in the brain to determine the quality of consciousness. It is worth noting that Freud's term for the ego was 'the I' and it was only in the standard translation from German that the term "the ego" became associated with Freud (1927). In everyday (lay) usage, "ego" has become synonymous with exaggerated self-confidence or an inflated ego/sense of self.

[5]A fully-developed, adult ego or sense of self.

[6]A network of functionally and structurally connected brain regions that show high spontaneous or "on-going" metabolism yet a relative deactivation during goal-directed cognition (Raichle et al., 2001).

[7]Functional connectivity is defined as temporal correlations between spatially distinct neurophysiological events (Karl Friston). Resting-state refers to task-free, unconstrained experimental conditions (typically sitting or lying still with eyes closed).

entropy-expansion (with a concomitant increase in system disorder) followed by entropy-suppression (or system re-organization and settling). Thus, the proposal that normal waking consciousness in healthy, adult, modern humans depends on entropy suppression implies that there was a state relatively proximal to this (e.g., in archaic homo-sapiens and in infants) in which entropy was relatively elevated, as it is in primary states. The point is that the brain of adult modern-humans is in a settling rather than expanding phase.

## THE RESEARCH VALUE OF PSYCHEDELICS

> "It does not seem to be an exaggeration to say that psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine or the telescope is for astronomy. These tools make it possible to study important processes that under normal circumstances are not available for direct observation." (Grof, 1980)

In 1953, the British research psychiatrist Humphrey Osmond was investigating the psychotomimetic (psychosis mimicking) effects of mescaline, a psychedelic drug derived from the peyote cactus. The British author Aldous Huxley learned of Osmond's work and struck up a correspondence, requesting that Osmond supervise a personal psychedelic experience. Huxley's subsequent mescaline experience would become the subject of his famous book "*The Doors of Perception*" (Huxley, 1954). Like many before and after him, Huxley was profoundly affected by his experiences with psychedelics and in 1956 sought with Osmond a satisfactory term for this class of drugs. At the time, "psychotomimetics" and "hallucinogens" were popular, but both men felt that these referred to mere aspects of the drug experience and not its essential character. Huxley suggested "phanerothyme," intending to mean "bringing forth the spirit or soul" (Huxley et al., 1977), and Osmond offered "psychedelic" combining the Greek words for "mind" or "soul" (psychē) with "dēlôsē," meaning "to manifest." While it was Osmond's "psychedelic" that would stick, it is telling that both men were searching for a word that could denote the same essential property, i.e., psychedelic's ability to make manifest latent aspects of the mind.

In 1943, Swiss chemist Albert Hofmann discovered the extraordinary psychological properties of lysergic acid diethylamide (LSD) (Hofmann, 1980) and the first reports on its effects appeared in scientific journals in the late 1940s. These papers immediately highlighted LSD's potential to be psychologically agitative. The first English language publication was released in 1950 and here the authors reported: "*the effect of LSD was a transitory toxic state, disturbing the barrier of repression and permitting a re-examination of significant experiences of the past that were sometimes relived with a frightening realism*." (Busch and Johnson, 1950) In the following years, psychedelics became one of the most researched classes of psychoactive drug in science, with several hundred relevant publications (Grinspoon and Bakalar, 1979). During these years, the focus shifted from psychedelics as psychotomimetics to psychedelics as psychotherapeutic adjuncts, with major international conferences on the topic (Grinspoon and Bakalar, 1979) and even the construction of purpose-built psychedelic treatment centers (Sandison, 2001). Political pressure in the late 1960s led to the illegalization of psychedelics and this had a significant negative impact on legitimate scientific research (Grinspoon and Bakalar, 1979; Lee and Shlain, 1985)—a problem that continues today (Nutt et al., 2013). Despite this however, there has been a resurgence of scientific interest in psychedelics in recent years (Vollenweider et al., 1998; Nichols, 2004; Griffiths et al., 2006, 2008; Moreno et al., 2006; Gonzalez-Maeso et al., 2007; Grob et al., 2011; Carhart-Harris et al., 2012a).

The dominant theoretical and therapeutic approach during the early era of psychedelic research was psychoanalytic. Psychedelics were used therapeutically under the rationale that they work to lower psychological defenses to allow personal conflicts to come to the fore that can then be worked through with a therapist (Cohen, 1972). A related model was that the relinquishment of "ego" enabled profound existential or "peak" experiences to occur that could have a lasting positive impact on behavior and outlook (Savage, 1962). Innumerable cases of apparent spontaneous insights about "self" or "nature" exist in the literature on psychedelics (Cattell, 1954; Sandison, 1954; Sandison and Whitelaw, 1957; Denber, 1958; Hausner and Dolezal, 1965; Torda, 1969; Cohen, 1972; Grof, 1982) and reports of "ego-dissolution" or "disintegration" are commonplace among those who have experienced the effects of these drugs (Carhart-Harris and Nutt, 2010; Carhart-Harris et al., 2012b). Some psychiatrists even believed that psychedelics could provide the necessary scientific evidence for major psychoanalytic hypotheses (Sandison, 1954; Cohen, 1972; Grof, 1982). For example, one enthused: "*The phenomenology of the psychodynamic experiences in LSD sessions is to a large extent in agreement with the basic concepts of classical psychoanalysis... Observations from LSD psychotherapy could be considered laboratory proof of the basic Freudian premises*." (Grof, 1982).

Psychoanalytic theory dominated psychiatry in the 1950s but after influential critiques (Eysenck, 1973), the cognitive revolution (Neisser, 1967) and significant pharmacological developments in psychiatry (Ban, 2001a,b; Fink, 2010), its influence significantly waned. As illustrated in **Figure 1**, despite over a century since its inception, psychoanalysis has failed to establish itself as a science of the mind. This may be because its hypotheses are hollow (Webster, 1995) or because they do not easily lend themselves to controlled experiment. In contrast, cognitive psychology is a mechanistic framework for describing observable phenomena that has become the natural bedfellow for human neuroscience. In comparison with the spectacular success of cognitive psychology, what should we make of the relative stagnancy of psychoanalysis? Is psychoanalysis scientifically redundant? Its fiercest critics claim that it is a belief system, a tautology with untestable hypotheses (Webster, 1995) but others claim that it has considerable explanatory value but could benefit from a closer integration with cognitive neuroscience (Kandel, 1999; Carhart-Harris and Friston, 2010; Panksepp and Solms, 2012). The present article takes this latter view and argues that the most realistic way forward for psychoanalysis as a science is for its most tangible hypotheses to be simplified and applied within the framework of cognitive neuroscience. Here we take the view that this is a necessary concession for psychoanalysis if it is to develop its credibility as a model of the mind.

In what follows, a roadmap is presented for how scientific research with psychedelics can assist the integration of psychoanalysis with cognitive neuroscience in order to further

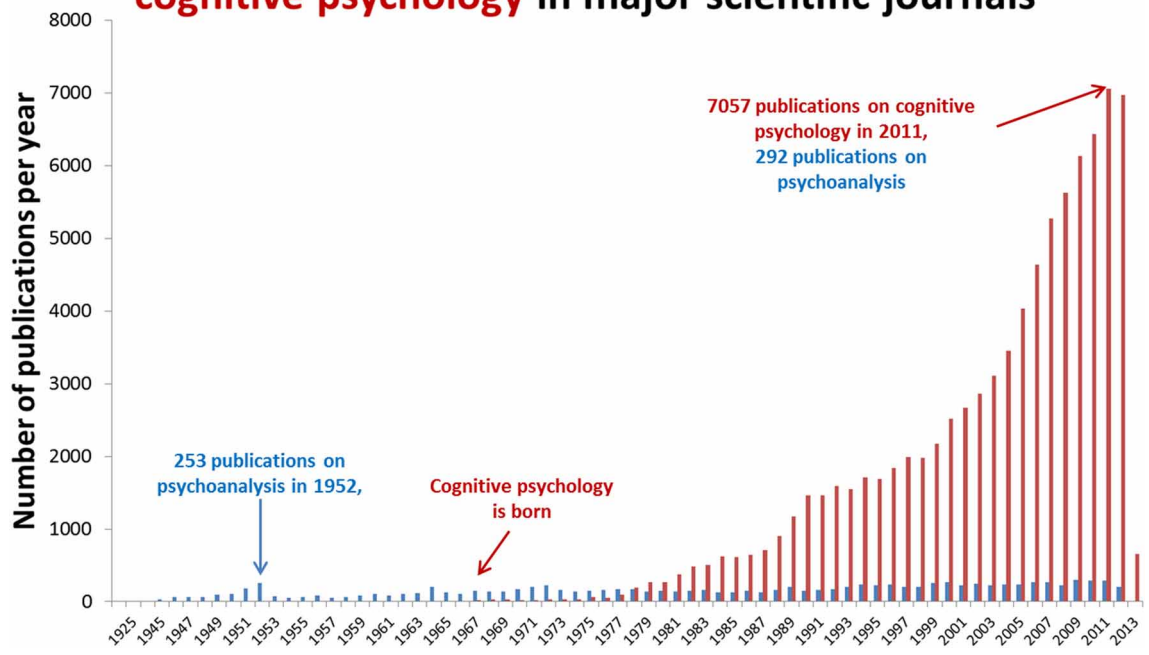


**FIGURE 1 | Relative publications on psychoanalysis and cognitive psychology.** Annual publications in major medical science journals referenced in the leading database, PubMed. Articles were retrieved by entering the search terms "psychoanalysis" and "cognitive psychology" in separate searches using the default search parameters of PubMed. It is worth noting that psychoanalysis has a different publication culture to cognitive neuroscience. Articles on psychoanalysis are not always available via PubMed and many psychoanalytic writings are published in books rather than academic journals. With these caveats entered however, the publication count shown above still helps to illustrate the general point that psychoanalysis has failed to gain a significant foothold in mainstream analytical science.

our understanding of human consciousness. This is motivated by the view that psychoanalysis can contribute something substantial to the mind sciences because it bridges an explanatory gap that has been left vacant by cognitive psychology. This gap only exists because cognitive psychology (rightly) focuses on phenomena that can be observed and manipulated by controlled experiment but crucially, *without psychedelic drugs, it is virtually impossible to bring the core phenomena of psychoanalytic theory into an observable space.*

Freud famously said of dreams that they provide privileged access to the workings of the unconscious mind (Freud, 1937) but research on dreaming is fraught with difficulties because [despite the phenomenon of lucid dreaming (Ogilvie et al., 1982)] the dream experience cannot be easily reflected on and reported in real-time, and neither can its onset and offset be easily controlled. Thus, Freud's cherished "royal road" has not proved particularly regal and a more practical alternative is required if key psychoanalytic theories are to be incorporated into the mind sciences.

> "If, as Freud said, dreams are the royal road to the unconscious, is it possible that psychedelic drugs are a superhighway to the unconscious?" (Holden, 1980)

This article argues that controlled studies with psychedelics are capable of providing major new insights into the nature of the mind and how it arises from brain activity. This is because the mind must be thoroughly deconstructed in order for us to become cognizant of its constituents and how they interact to give rise to global phenomena. The unique scientific value of psychedelics rests on their ability to selectively target processes that appear to be critical for the maintenance of normal waking consciousness. In addressing the action of psychedelic drugs on the brain, this article begins at the cellular level before progressing to the systems level. The intention is to offer a comprehensive account of how psychedelics alter brain function to alter consciousness.

Somewhat uniquely, psychedelics can be studied at a range of epistemological levels; from molecular pharmacology (Gonzalez-Maeso and Sealfon, 2009) to psychoanalytic psychology (Cohen, 1964; Grof, 1982), few topics can engage scientists from as wide a range of disciplines. This reflects not only the special research value of psychedelics but also the immensity of the challenge involved in understanding them; especially, if the intention is to develop a comprehensive account of how psychedelics affect the brain to alter consciousness. The present article should therefore be read with an acknowledgement that this quest is on-going.

Before we begin, it is necessary to enter some important caveats. Firstly, it needs to be stated that those looking for evidence for the authenticity of aspects of Freudian theory will be left dissatisfied by this article. Categorically, this is not its aim. This

challenge requires a thorough review of the phenomenology of relevant altered states of consciousness (e.g., the psychedelic state) and this is something that has been attempted before (Carhart-Harris, 2007; Carhart-Harris and Friston, 2010). Thus, due to space limitations, this article's treatment of the relevant phenomenology is relatively superficial. Instead it places its focus on the system-level mechanics of the psychedelic state as an exemplar of a regressive[8] style of cognition that can also be observed in REM sleep and early psychosis.

Some proponents of psychoanalysis may feel that this mechanistic approach has little relevance to psychoanalysis in its hermeneutic or interpretative guise. However, the inherent subjectivity of this aspect of psychoanalysis means that it is difficult to see how it can ever significantly impinge on the scientific study of the mind and brain. Indeed, Freud acknowledged that it was his "metapsychology" that had the most to offer science (Freud, 1949), and at least as a first step, this is where psychoanalytic theory (rather than psychoanalytic practice) should look to develop its scientific credibility. Briefly, for readers who are unfamiliar with Freudian metapsychology and wish to understand it better, his original material should be read (e.g., Freud, 1927, 1949; Freud et al., 1957) and the following review articles may be useful (Carhart-Harris et al., 2008; Carhart-Harris and Friston, 2010). For those interested in the rich phenomenology of the psychedelic experience and how this relates to Freudian and/or Jungian descriptions of "the unconscious mind," the following references may be of interest (Sandison and Whitelaw, 1957; Huxley, 1959; Cohen, 1964; Grof, 1982; Merkur, 1998; Sandison, 2001). Lastly, it is necessary to state that questions related to the safety of scientific research with psychedelics will not be addressed here. However, evidence strongly supports the position that, conducted with appropriate caution, research with psychedelics presents a low risk of harm to study participants (Johnson et al., 2008; Morgan et al., 2010; Carhart-Harris and Nutt, 2010; Studerus et al., 2011; van Amsterdam et al., 2011).

## THE PHARMACOLOGY OF PSYCHEDELICS

Before introducing the focal topic of this paper, i.e., entropy and its relation to key brain imaging parameters, it is important to provide a brief introduction to the pharmacology of psychedelics. By definition, all *classic* psychedelic drugs are agonists at the serotonin 2A receptor (5-$HT_{2A}$R) (Glennon et al., 1984). There is a strong positive correlation between a psychedelic's affinity for the 5-$HT_{2A}$R and its psychedelic potency (Glennon et al., 1984). For example, LSD has a very high affinity for the 5-$HT_{2A}$R and is remarkably potent, being psychoactive in doses as small as 20 μM (Hintzen and Passie, 2010). Blockade of the 5-$HT_{2A}$R with the 5-$HT_{2A}$R antagonist ketanserin, attenuates the principal hallucinogenic effects of psilocybin in humans (Vollenweider et al., 1998). The 5-$HT_{2A}$R is primarily expressed in the cortex (Pazos et al., 1987). In humans, the distribution of 5-$HT_{2A}$Rs is generally high throughout the cortex but is densest in high-level association regions such as the PCC and lowest in the primary motor cortex (Erritzoe et al., 2009; Carhart-Harris et al., 2012a). This may explain why cognition and perception are so markedly affected by psychedelics whereas motor action is generally not. In terms of the cortex's laminar organization, 5-$HT_{2A}$Rs are most densely expressed postsynaptically on the apical dendrites of layer 5 pyramidal neurons (Weber and Andrade, 2010). These large excitatory neurons are the primary source of output from a cortical region, projecting to hierarchically subordinate cortical and subcortical regions (Spruston, 2008). 5-$HT_{2A}$R stimulation depolarizes the host cell, making it more likely to fire (Andrade et al., 2011) and this effect has been demonstrated in layer 5 pyramidal neurons in rodents (Aghajanian and Marek, 1997).

## FUNCTIONAL MRI AND MEG STUDIES WITH PSILOCYBIN

Beginning in 2009, our research team embarked on a series of studies with the classic psychedelic, psilocybin (Carhart-Harris et al., 2012a), culminating in a recent MEG study (Muthukumaraswamy et al., 2013). Our first study utilized arterial spin labeling (ASL), an fMRI technique that measures changes in CBF. Specifically, we compared CBF before and after intravenous (i.v.) administration of 2 mg psilocybin and placebo (Carhart-Harris et al., 2012a). The onset of the subjective effects of psilocybin is rapid when it is administered intravenously, commencing within seconds of the end of the infusion (Carhart-Harris et al., 2011). The infusion occurred over 60 s, beginning 6 min into an 18 min resting state scan. Drug-induced changes in CBF were modeled based on psilocybin's rapid pharmacodynamics (Carhart-Harris et al., 2011). Fifteen healthy volunteers were scanned and the results revealed decreased CBF after psilocybin and no increases. The decreases were localized to high-level association cortices, including key regions of the DMN (see Some background on the default mode network (DMN) for an overview of this system) and subcortical hub structures such as the putamen and thalamus (Carhart-Harris et al., 2012a).

These findings were later replicated using the classic BOLD signal of fMRI. Another 15 healthy volunteers were scanned using a similar placebo-controlled design, with 60 s i.v. infusions beginning midway through two separate 12 min eyes-closed resting state scans on different days. Again, only signal decreases were observed after drug infusion. Moreover, the location of the BOLD signal decreases was consistent with the CBF decreases, e.g., in midline cortical nodes of the DMN (Muthukumaraswamy et al., 2013).

In addition to modeling changes in the direction of the BOLD signal post-infusion of psilocybin, we also measured changes in brain network integrity using resting-state functional connectivity. Three regions of interest were chosen for separate seed-based resting state functional connectivity (RSFC) analyses: a medial prefrontal cortex (mPFC) seed, a right middle frontal gyrus (mFG) seed, and a bilateral hippocampal seed. Decreased connectivity was observed within the DMN using the mPFC and hippocampal seeds and in a major task-positive network (TPN), the dorsal attention network (DAN), using the mFG seed (**Figure 2**).

In our third and most recent study, we used MEG to investigate the effects of psilocybin on neural activity. Broadband decreases in oscillatory power were observed after psilocybin, and again, these were localized to association cortices, including key regions of the DMN, such as the PCC (Raichle et al., 2001; Greicius et al., 2003)—see **Figure 2**.

[8]The quality of returning to an earlier state of development.

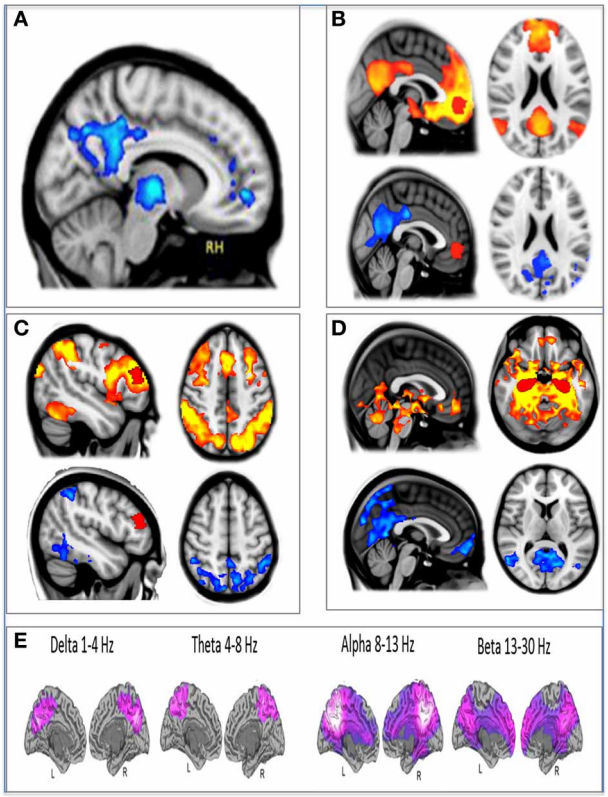


**FIGURE 2 | The effect of psilocybin on fMRI and MEG measures of brain activity. (A)** Decreased CBF post-psilocybin. **(B)** Ventromedial PFC (red) resting state functional connectivity (RSFC) at baseline (top, orange) and decreases post-psilocybin (bottom, blue). **(C)** Dorsolateral PFC (red) RSFC at baseline (top, orange) and decreases post-psilocybin (bottom, blue). **(D)** Hippocampal (red) RSFC at baseline (top, orange) and decreases post-psilocybin (bottom, blue). **(E)** Decreases in oscillatory power (purple) post-psilocybin measured with MEG. All spatial maps were whole-brain cluster corrected $Z > 2.3$. $p < 0.05$.

These studies provide some useful clues about the mechanisms by which psychedelics alter brain function to alter consciousness. They imply that cerebral blood flow, BOLD signal, functional connectivity and oscillatory power are decreased in brain regions that are normally highly metabolically active, functionally connected and synchronous/organized in their activity. These results provided the kernel for our subsequent thinking about increased entropy in the psychedelic state. Although none of the analyses formally measured entropy, they spoke to a general principle that psychedelics alter consciousness by *disorganizing* brain activity.

## SOME BACKGROUND ON THE DEFAULT MODE NETWORK

The DMN has become one of the most discussed topics in cognitive neuroscience over the last decade and there are several reasons why it is justified to consider it important (Guldenmund et al., 2012). DMN regions receive more blood flow (Zou et al., 2009) and consume more energy (Raichle and Snyder, 2007) than other brain regions. Indeed, CBF and metabolic rate are approximately 40% higher in the PCC than the average of the rest of the brain (Raichle et al., 2001). The magnitude of the DMN's energy consumption dwarfs the comparatively trivial energy changes induced by stimulus cues (Raichle, 2006, 2010). DMN regions are centers of dense connectivity (Hagmann et al., 2008), implying that they serve as important connector hubs for information integration and routing (van den Heuvel et al., 2012). Consistent with this, a major node of the DMN, the PCC, can be spatially segmented into sub-components that functionally couple to different brain networks (Leech et al., 2012). Similarly, during transient windows of especially high internal coupling (functional connectivity) within the DMN, coupling between the DMN and other brain networks is also markedly increased (de Pasquale et al., 2012). Importantly, this functional centrality of the DMN is not shared by other brain networks (de Pasquale et al., 2012; Braga et al., 2013), implying that, as the highest level of a functional hierarchy (Carhart-Harris and Friston, 2010), it serves as a central *orchestrator* or *conductor* of global brain function. Functionally, the DMN is relatively removed from sensory processing (Sepulcre et al., 2012) and is instead engaged during higher-level, metacognitive operations such as self-reflection (Qin and Northoff, 2011), theory-of-mind (Spreng and Grady, 2010) and mental time-travel (Buckner and Carroll, 2007)—functions which may be exclusive to humans. DMN connectivity increases through development from birth to adulthood (Fair et al., 2008; Gao et al., 2009) and DMN regions have undergone significant evolutionary expansion (Van Essen and Dierker, 2007). Despite our knowledge of these things however, it is poorly understood why the DMN consumes so much of the body's energy (Raichle and Mintun, 2006). This uncertainty regarding the nature of the DMN's disproportionate energy consumption has led to loose analogies being made between it and the *dark energy* of cosmology (Raichle, 2006, 2010). It is consistent with the hypotheses of this paper to suggest that this apparent excess energy of apparently unknown function, residing in the DMN, is in fact the physical counterpart of the narrative-self or ego—much of which is indeed unconscious or implicit.

## INTRODUCING PRIMARY CONSCIOUSNESS AND PRIMARY STATES

This article proposes that states such as the psychedelic state, REM sleep, the onset-phase of psychosis and the dreamy-state of temporal lobe epilepsy are examples of a regressive style of cognition that is qualitatively different to the normal waking consciousness of healthy adult humans. We will refer to this mode of cognition as "primary consciousness"[9] and the states themselves as "primary states." To enter a primary state from normal waking consciousness, it is proposed that the brain must undergo a "phase transition" (Zeeman, 1973; Waddington, 1974), just as there must have been a phase-transition in the evolution of human consciousness with the relatively rapid development of the ego and its capacity for metacognition[10]. This implies that the relationship between normal waking consciousness and "primary consciousness" is not perfectly continuous.

[9]A regressive, pre-ego style of consciousness characterized by unconstrained brain dynamics and cognition. The psychedelic state is an exemplar of primary consciousness and REM sleep and early psychosis are others.

[10]A cognitive capacity unique to adult humans and dependent on the formation of a mature ego. Metacognition means "cognition about cognition." Examples include: self-reflection, theory-of-mind and mental time-travel. (Fleming et al., 2012).

Freud was a great admirer of Darwin and made several references to him throughout his work (Freud et al., 1953). Indeed, Freud considered his own hypotheses to be natural deductions from evolutionary theory. He argued that dreaming and psychosis typify a primitive style of thinking that is dominant in human infancy[11] and dominated the cognition of primordial man[12], preceding the development of the ego of modern adult humans. Primitive thinking is fundamentally different to the style of cognition possessed by healthy adult humans. This is because in healthy adults, the formation of a mature ego endows the mind with a capacity for metacognition i.e., an ability to reflect on one's own thoughts and behavior (Shimamura, 2000; Fleming et al., 2012).

These ideas form the core of this article's hypotheses. Thus, it is appropriate to clarify them here. A distinction is being made between two fundamentally different styles of cognition, one that is associated with the consciousness of mature adult humans, and another that is a mode of thinking the mind regresses to under certain conditions, e.g., in response to severe stress, psychedelic drugs and in REM sleep. The style of cognition that is dominant in normal waking consciousness will henceforth be referred to as *secondary consciousness*[13] and the (pre-ego) style of cognition that is associated with primitive states will be referred to as *primary consciousness*. It is acknowledged that these terms have been used before (Edelman, 2004) but their meaning in the present context is largely independent.

Consistent with Karl Friston's free-energy principle (Friston, 2010), this article takes the view that the mind has evolved (via secondary consciousness upheld by the ego) to process the environment as *precisely* as possible by finessing its representations of the world so that *surprise* and *uncertainty* (i.e., entropy) are minimized. This process depends on the ability of the brain to organize into coherent, hierarchically-structured systems (Bassett et al., 2008; Friston, 2010), critically poised between order and disorder (Friston et al., 2012b; Schwartenbeck et al., 2013). In contrast, in primary states, cognition is less meticulous in its sampling of the external world and is instead easily biased by emotion, e.g., wishes and anxieties.

Later we finesse this basic model, arguing that secondary consciousness actually depends on the human brain having developed/evolved a degree of sub-criticality in its functionality, i.e., an extended ability to suppress entropy and thus organize and constrain cognition. It is argued that this entropy-suppressing function of the human brain serves to promote realism, foresight, careful reflection and an ability to recognize and overcome wishful and paranoid fantasies. Equally however, it could be seen as exerting a limiting or narrowing influence on consciousness.

This paper argues that the underlying neurodynamics of primary states are more "entropic" than secondary states i.e., primary states exhibit more pronounced characteristics of criticality and perhaps supercriticality than normal waking consciousness—implying that the latter is slightly sub-critical, if not perfectly critical. Secondary consciousness pays deference to reality by carefully sampling the world and learning from its encounters (Friston, 2010), whereas primary consciousness does this more haphazardly. Mechanistically, whereas the brain strives toward organization and constraint in secondary consciousness, processes are more flexible in primary consciousness. Freud outlined these ideas in his writings on "the reality principle" (Freud, 1927) and they are recast here in a more mechanistic form, tied to modern cognitive neuroscience.

The phenomenon of "magical thinking"[14] (Frazer, 1900; Subbotskii, 2010; Hutson, 2012) is a potential product of primary consciousness. Magical thinking is a style of cognition in which supernatural interpretations of phenomena are made. Magical thinking is more likely in situations of high uncertainty because there is a greater opportunity for dreaming up explanations that lack an evidence base (Friston, 2010). Wishful beliefs are a classic product of magical thinking because they interpret the world according to what an individual *wants* to be true (in Freudian terms, they adhere to the pleasure principle). Wishful inferences are quick-fixes that reduce uncertainty but via simplistic explanations that satisfy fancies or desires before careful reason. Another example of magical thinking is paranoia; in this case, an individual jumps to negative conclusions about a situation, even in the face of contradictory evidence, because to do so effectively suspends uncertainty while providing some narcissistic satisfaction. The popularity of magical thinking also suggests that there is some enjoyment in uncertainty, perhaps because it promotes imaginative and creative thinking—and that this is associated with positive affect.

In the forthcoming section we discuss the relationship between medial temporal lobe (MTL—i.e., specially the hippocampus and surrounding parahippocampal structures) activity and primary consciousness, highlighting a specific change in activity that may serve as a marker of primary states.

## THE MEDIAL TEMPORAL LOBES AND PRIMARY CONSCIOUSNESS

Recording directly from MTL circuits in different altered states presents a significant challenge for cognitive neuroscience, but not one that should deter us from trying to expand its reach into areas of relevance to psychoanalytic theory. Pioneering surgical interventions for epilepsy and Alzheimer's disease (Axmacher et al., 2008, 2010; Fell et al., 2011, 2012; Laxton and Lozano, 2012) are opening up new possibilities for depth recordings, and although it would be a challenge to defend the administration of psychedelics to such patients, recording from MTL circuits in other primary states, such as REM sleep, might be more feasible (Cantero et al., 2003).

Another way to circumvent the problem of recording directly from limbic regions is to use non-invasive imaging with high spatial resolution. We recently used fMRI to investigate the involvement of the MTLs in the mechanism of action of psychedelics, performing a hippocampal functional connectivity analysis using

[11] The term "infancy" is used here in an extended sense to mean the period from birth to two years of age.

[12] The earliest humans, i.e., archaic homo-sapiens.

[13] The style of consciousness of healthy, adult, modern humans during waking. Secondary consciousness is "constrained" relative to primary consciousness, both in a mechanistic and qualitative sense.

[14] A style of cognition in which causal relationships between phenomena are assumed despite an absence of supportive scientific evidence. Examples include superstition, and metaphysical beliefs. Crucially, such beliefs usually honor an emotional sentiment such as a wish (or fear) that something is true.

the same psychophysiological interaction (PPI) model used in our previous analyses with psilocybin (Carhart-Harris et al., 2012a). A combined bilateral hippocampal and parahippocampal mask was created on a standard brain and time-series were extracted from these regions for each subject and regressed against their functional data, with the pharmacodynamics of intravenous psilocybin modeled as an interaction term. Remarkably, decreases in functional coupling were observed after psilocybin that were selectively localized to the cortical nodes of the DMN (**Figure 2D**), entirely consistent with the hypothesis that decreased MTL-DMN coupling underlies phase transitions to primary consciousness.

In a separate analysis, we looked at changes in BOLD signal variance (i.e., amplitude fluctuations) after psilocybin and found significant increases in variance that were almost exclusively localized to the bilateral hippocampi and parahippocampal gyri. This result was important because it reinforced the impression given by the RSFC analysis that under psilocybin, the hippocampi become decoupled from the DMN. However, perhaps even more interestingly, the increase in MTL signal variance was consistent with some early depth electrode work with psychedelics that implicated the MTLs in their mechanism of action. This work is reviewed below.

Human depth recordings involving the insertion of electrodes into structures located deep in the brain (Ramey and O'Doherty, 1960) were not uncommon in the 1950s and 60s. Remarkably, some intracranial recordings were carried out during this period in individuals administered LSD and mescaline (Schwarz et al., 1956; Monroe et al., 1957; Monroe and Heath, 1961). The relevant reports document unusual phasic activities in the MTLs during the drug state that were difficult to detect at the scalp. Moreover, in separate studies, temporal lobectomy was found to abolish the effects of LSD in humans (Serafetinides, 1965) and chimpanzees (Ramey and O'Doherty, 1960) and frontal lobotomy was found to augment them (Keup, 1970). Further support for the involvement of MTLs in the mechanism of action of psychedelics comes from reports of similar phasic limbic activity in other altered states of consciousness that show phenomenological similarities with the psychedelic state, namely: REM sleep, acute psychosis and the so-called "dreamy-state" of temporal lobe epilepsy and electrical stimulation of the MTL (Carhart-Harris, 2007; Carhart-Harris and Friston, 2010). Importantly, these states are all characterized by a particular style of cognition that is fundamentally different from that of normal waking consciousness.

It is proposed here that coupling between the MTLs and the cortical regions of the DMN is necessary for the maintenance of adult normal waking consciousness, with its capacity for metacognition. Moreover, a breakdown in hippocampal-DMN coupling is necessary for a regression to primary consciousness. These hypotheses are motivated by our finding that DMN-hippocampal coupling is decreased under psilocybin (**Figure 3D**), and while DMN activity becomes desynchronous and therefore disorganized (**Figure 3E**), the amplitude of BOLD signal fluctuations increases in the hippocampus (**Figure 2**).

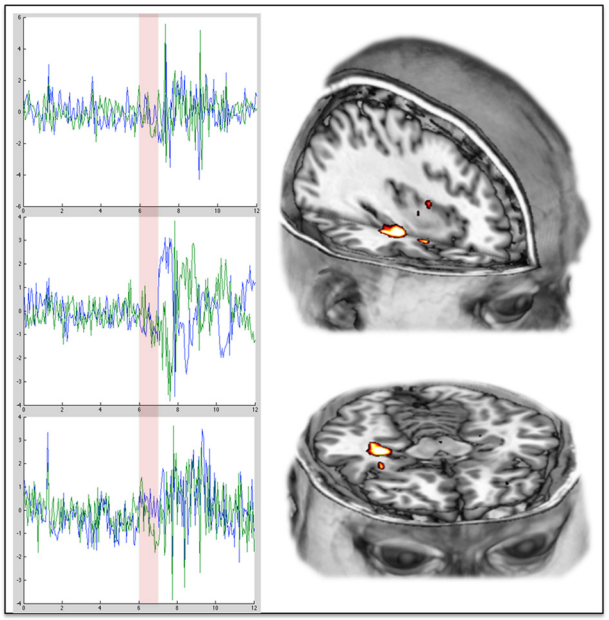

**FIGURE 3 | Increased variance/amplitude fluctuations in the hippocampus post-psilocybin.** The charts on the **left** show the complete time series from the hippocampus (**left** in blue, **right** in green) in 3 different individual subjects during the 12 min scan in which they received psilocybin. The transparent red vertical line indicates the beginning and duration of the 60 s infusion of psilocybin. The images on the **right** show the **right** hippocampal region where the increases in variance were especially marked.

## THE DEFAULT MODE NETWORK AND THE EGO

Layer 5 pyramidal neurons densely express 5-$HT_{2A}$ receptors (Weber and Andrade, 2010). These cells are an important target of psychedelics (Aghajanian and Marek, 1997) and are known to fire with an intrinsic alpha frequency (Silva et al., 1991; Sun and Dan, 2009). Alpha oscillations are thought to be related to temporal framing in perceptual processing (Lorincz et al., 2009; Klimesch et al., 2011) but more intriguingly given the focus of the present article, a positive relationship has been found between self-reflection and alpha power (Knyazev et al., 2011) and alpha synchronization during rest and Blood Oxygen Level Dependent (BOLD) activity in regions of the DMN (Jann et al., 2009). Evidence implicates the DMN in self-reflective and introspective functions (Qin and Northoff, 2011) and the phase of fluctuating activity in the DMN is often inversely correlated (or "anticorrelated") with fluctuating activity in networks concerned with task-focused attention (task-positive networks, TPNs) (Fox et al., 2005). Like the DMN, alpha oscillations mature developmentally and evolutionarily (Basar and Guntekin, 2009), tempting speculations that these rhythms have developed to reduce "entropy" [i.e., disorder or uncertainty (Ben-Naim, 2008)] by increasing mutual information among neuronal ensembles (Tononi et al., 1994; Basar and Guntekin, 2009). With this in mind, it was remarkable that we recently found a highly significant positive correlation between the magnitude of alpha power *decreases* in the PCC after psilocybin and ratings of the item "I experienced a disintegration of my 'self' or 'ego'." Scores on this item also correlated positively with decreases in delta, theta, beta, and low gamma power, although alpha explained the most variance (a considerable 66%) see **Figure 4**. Twenty three subjective items

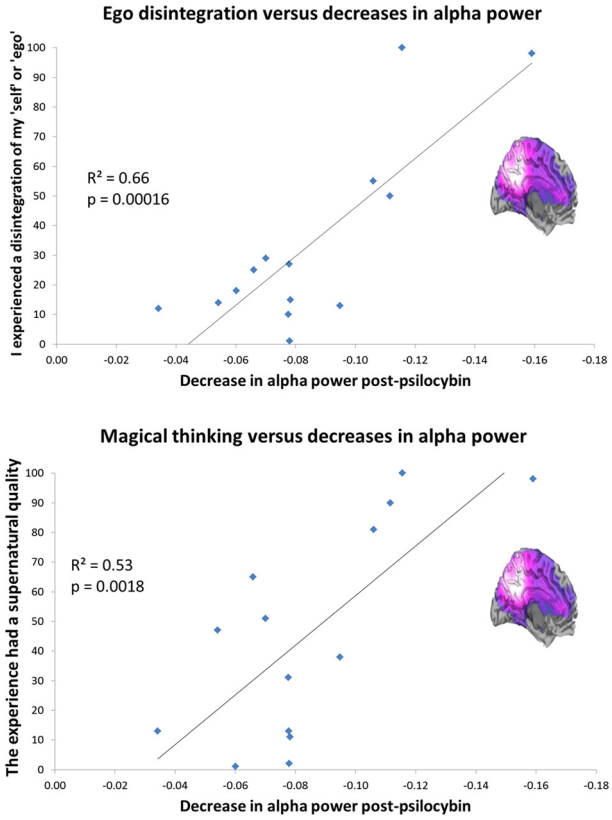


**FIGURE 4 | Decreased PCC alpha power predicts ego-disintegration and magical thinking after psilocybin. Top:** Decreased PCC alpha power *v* ratings of ego-disintegration. **Bottom:** Decreased PCC alpha power vs. ratings of magical/supernatural thinking. Both correlations were significant after correction for multiple comparisons (0.05/23 = 0.002). These charts are derived from data discussed in Muthukumaraswamy et al. (2013).

were rated after psilocybin but the one enquiring about ego-disintegration showed the closest relationship with the decreases in alpha power, surviving the conservative Bonferroni correction for multiple comparisons. Interestingly, the only other item that survived correction for multiple comparisons referred to the promotion of magical thinking, i.e., "the experience had a supernatural quality." It is a central hypothesis of this paper that psychedelics induce a primitive state of consciousness, i.e., "primary consciousness" by relinquishing the ego's usual hold on reality (DMN control on MTL activity).

The organizing influence of alpha applies more generally to oscillatory rhythms in the brain (Salinas and Sejnowski, 2001; Buzsaki and Draguhn, 2004). Harmonics are known to exist between the brain's oscillatory rhythms, with higher frequency oscillations "nested" within lower frequencies (Jensen and Colgin, 2007). For example, intracranial recordings from the ventral PCC in humans revealed a dominant presence of theta oscillations. The phase of these oscillations modulate the amplitude of high-gamma oscillations and the magnitude of this coupling fluctuates at a frequency that is consistent with that of spontaneous BOLD signal fluctuations (i.e., ∼0.1 Hz) observed in resting-state networks (RSNs) such as the DMN (Foster and Parvizi, 2012). Theta oscillations are a canonical rhythm of hippocampal circuits, at least in rodents (Buzsaki, 2002), and MTLs are known to be strongly connected to the PCC (Parvizi et al., 2006) and DMN more generally (Kahn et al., 2008). Thus, it is feasible that a function of PCC theta oscillations is to constrain the activity of limbic circuits, which reciprocally input to the PCC. Evidence that MTL activity exerts a *driving* influence on PCC activity comes from a recent report on deep brain stimulation for Alzheimer's disease. Chronic stimulation of the fornix, an important component of hippocampal circuitry, was associated with significantly increased glucose metabolism in the PCC (Laxton et al., 2012).

In summary, interaction between different oscillatory rhythms introduces a structured quality to brain activity (Rumsey and Abbott, 2004), constraining the naturally stochastic firing of individual pyramidal neurons (Rolls and Deco, 2010) and so providing ideal conditions for the emergence of "complexity" (Tononi et al., 1994) or "self-organized criticality" (Jensen, 1998). A key hypothesis of this article is that it is through the development of self-organized activity in the DMN [and concomitant entropy/uncertainty/disorder minimization (Friston, 2010)] that a coherent sense of self or "ego" emerges (Carhart-Harris and Friston, 2010). This process of maturational settling succeeds an earlier state of elevated entropy (primary consciousness) and psychedelic drugs induce a regression to this entropic brain state via the mechanisms outlined above.

With these foundations laid, the following hypotheses can be proposed: (1) coupling within the DMN, and *especially* between the MTL and DMN, is a characteristic of maturational settling that is necessary for secondary consciousness and the development of an integrated sense of self; (2) a relative decoupling within the DMN and specifically between the MTLs and DMN occurs when secondary consciousness abates and there is a reciprocal increase in the influence of primary consciousness; (3) decreased MTL-DMN coupling allows the MTLs to function more independently of the DMN and this can result in unusual MTL activities such as have been recorded with depth electrodes in primary states (see above and Grof, 1982; Bassett et al., 2008; Axmacher et al., 2010) and may have been detected in the BOLD signal amplitude increases in the MTL post-psilocybin (**Figure 3**); (5) unconstrained/disinhibited/anarchic MTL activity is a principal characteristic of primary states and the occurrence of these activities is consistent with a system at criticality; (6) brain activity in primary consciousness is closer to criticality-proper than it is during normal waking consciousness (which may be slightly sub-critical rather than perfectly critical).

## THE DMN, INTROSPECTION AND METACOGNITION

DMN resting-state functional connectivity correlates positively with ratings of internal awareness (Vanhaudenhuyse et al., 2011), depressive rumination (Berman et al., 2011) and trait neuroticism (Adelstein et al., 2011). DMN connectivity increases during mental time-travel (Andrews-Hanna et al., 2010; Martin et al., 2011) and activity in the medial prefrontal node of the DMN is reliably elevated in depression (Farb et al., 2011; Lemogne et al., 2012). These findings strongly implicate the DMN in introspective thought and suggest that hyper activity and

connectivity in the DMN is related to a certain style of *concerted* introspection.

To step back, one of the primary hypotheses being developed here is that metacognition, and in particular, the human capacity for self-reflection, is an advanced behavior that rests on self-organized activity in the DMN and between the DMN and the MTLs. Thus, if the DMN is hyper-active and connected in depression, does this imply that mild depression is an evolutionarily advanced state? The phenomenon of "depressive realism" has been recognized for several decades (Dykman et al., 1989; Haaga and Beck, 1995) and sits comfortably with the idea that a primary function of the DMN is to support metacognition (Fleming et al., 2010). The suggestion is that increased DMN activity and connectivity in mild-depression promotes concerted introspection and an especially diligent style of reality-testing. However, what may be gained in mild depression (i.e., accurate reality testing) may be offset by a reciprocal decrease in flexible or divergent thinking (and positive mood).

The proposal that increased DMN activity and connectivity is a key functional correlate of concerted introspection, such as is seen in depression, may seem inconsistent with the association between DMN activity and mind-wandering (Mason et al., 2007) but this is a conceptual problem that can be easily resolved. The positive relationship between increased BOLD signal in the DMN and the frequency of mind-wandering during task-performance (Mason et al., 2007) tells us nothing about the nature or *style* of the cognition in the off-task state, it simply tells us that the mind has drifted off-task. It is known however, that the strength of inverse coupling between activity in the DMN and TPNs is increased when task performance is more consistent (Kelly et al., 2008), implying increased focus and a relative decrease in off-task attentional lapses. DMN-TPN inverse coupling is decreased in patients with attention deficit/hyperactivity disorder (ADHD) (Hoekzema et al., 2013) and increased after administration of the attention-enhancers modafinil (Schmaal et al., 2013) and nicotine (Cole et al., 2010). Thus, it is too simplistic to regard increased BOLD signal in the DMN as a correlate of freely-wandering cognition, and decreased inverse coupling between the DMN and TPN is probably a more informative index of this. As will be discussed later, this point is reinforced by findings that inverse coupling between the DMN and TPNs is decreased under psilocybin, and DMN activity and connectivity is also decreased. This is important because unconstrained, explorative thinking is a hallmark of the psychedelic state (see **Figure 5**).

In the next section we cite direct evidence for increased entropy in brain networks in psychedelic state and use this to support a general principle: that the transition from normal waking consciousness to primary consciousness is marked by an increase in system entropy.

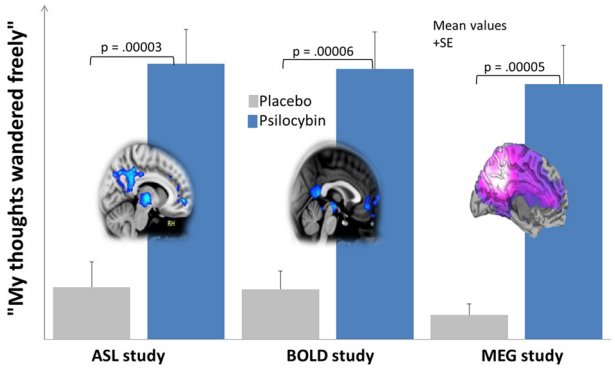


**FIGURE 5 | Psilocybin promotes unconstrained thinking and decreases blood flow, venous oxygenation and oscillatory power in the DMN.** This chart shows the average (+*SE*) ratings for the item "my thoughts wandered freely" in 3 neuroimaging studies, each involving the administration of psilocybin and placebo to 15 healthy volunteers. Ratings were given within 30 min of the end of the relevant resting state scans. This particular item was one of the highest rated items in all 3 studies and nicely communicates the quality of cognition that predominates in the psychedelic state. The brain image on the left displays the mean regional decreases in CBF post-psilocybin in the ASL study; the central image displays the mean regional decreases in BOLD signal post-psilocybin in the BOLD study; and the image on the right displays the mean regional decreases in alpha power post-psilocybin in the MEG study. All images were derived using a whole brain corrected threshold of $p < 0.05$.

## INCREASED NETWORK ENTROPY IN THE PSYCHEDELIC STATE

There is an emerging view in cognitive neuroscience that the brain self-organizes under normal conditions into transiently stable spatiotemporal configurations (Sporns et al., 2004; Shanahan, 2010; Deco and Corbetta, 2011; Tagliazucchi et al., 2012) and that this instability is maximal at a point where the global system is critically poised in a transition zone between order and chaos (Tononi et al., 1994; Shanahan, 2010; Deco and Jirsa, 2012; Tagliazucchi et al., 2012). In the present context, the "metastability" (Tognoli and Kelso, 2014) of a brain network is a measure of the variance in the network's intrinsic synchrony over time. That is, if the signal in all of the voxels within a given network deviates little from the network's mean signal, then variance is low, whereas if the signal in voxels fluctuate erratically, then variance is high. Thus, using the data from the BOLD fMRI study with psilocybin, we recently looked at changes in the variance of intra-network synchrony over time in nine canonical resting-state networks (Smith et al., 2009) pre and post placebo and psilocybin. Results revealed significantly increased network variance in high-level association networks after psilocybin but not in sensory specific and motor networks, and there were no changes after placebo. These results imply that activity in high-level networks becomes relatively disorganized under psilocybin, consistent with the entropic brain hypothesis.

To translate this result into a formal measure of entropy, we discretized the time course of intra-network synchrony over time into equal sized bins where each time-point could be entered into a bin depending on the variance in the network's synchrony at that time point. Doing this for each network, we built probability distributions of the variance of the intra-network synchrony across time from which we could then calculate the Shannon entropy for each network. Not surprisingly, increased entropy was observed in the networks in which there was increased

variance post-psilocybin i.e., the high-level association networks (See **Figure 6**).

To further assess entropy changes after psilocybin, we took a slightly different approach. Four regions were chosen from a limbic/paralimbic system based on prior knowledge that BOLD signal variance was increased in these regions under psilocybin. The regions included: the left and right hippocampi and the left and right anterior cingulate cortex (ACC). A threshold was set for connection strength such that only connections above a particular strength survived and were therefore said to "exist." This allowed functional connectivity motifs (connectivity graphs) to be identified at each time point in the time series. With 4 nodes, there were 64 possible connectivity motifs or graphs at any given time point. The results revealed a greater repertoire of motifs

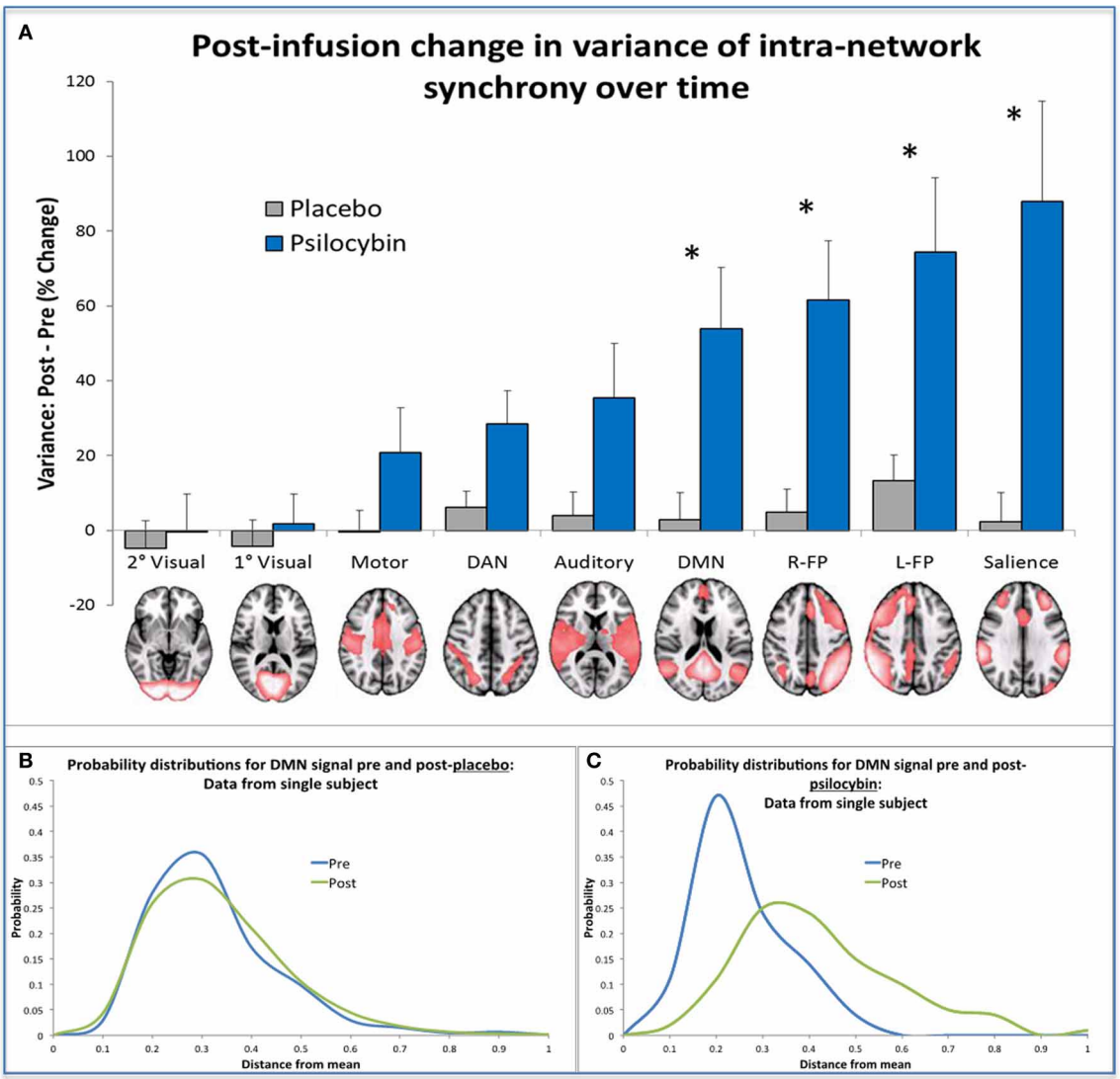


**FIGURE 6 | Changes in network metastability and entropy post-infusion of psilocybin. (A)** This chart displays the mean variance of the internal synchrony of 9 brain networks for the sample of 15 healthy volunteers, as a percentage change post vs. pre-infusion. A post-infusion increase in metastability for a specific network indicates that the mean signal in that network is a poor model of the activity in its constituent voxels, implying that the network is behaving more "chaotically" post-infusion than pre. Bonferonni correction gave a revised statistical threshold of $p < 0.006$ (0.05/9). One-sample (2-tailed) *t*-tests were performed, comparing the % change against zero. The significant networks are labeled with an asterisk. **(B,C)** These probability distributions were derived from data from the same single subject, by discretizing a measure of the internal synchrony of the DMN across time into bins. These bins reflect the distance a data point is from the mean and this gives a probability distribution of the variance of internal synchrony within a network for a given time period (e.g., a 5 min period of scanning). The probability distributions shown in **Chart B** were produced from placebo data where it is clear that prediction of internal network synchrony of the DMN across time is similar before and after infusion (i.e., the blue and green curves). The probability distributions shown in **Chart C** were derived using psilocybin data and here it is evident that following infusion of psilocybin (i.e., the green curve), prediction of internal network synchrony within the DMN is more difficult compared to pre infusion (the blue curve). When the entropy change was calculated for the group, significantly greater increases in entropy were found in the same networks highlighted in **(A)** (post-psilocybin vs. pre) vs. (post-placebo vs. pre).

under psilocybin than either at baseline or after placebo. Indeed, a number of motifs were exclusive to the psilocybin condition. The entropy of a time series could then calculated by assessing the entropy of a sequence of motifs over a period of time (i.e., how easy/difficult is it to predict a sequence of motifs in a given state?). This is the same procedure one would follow in order to calculate the entropy of a transcribed passage of speech for example (i.e., the likelihood of certain words occurring in a coherent passage is not random, e.g., some words, such as "I," occur much more often than others). Thus, it was found that the sequence of motifs had significantly greater entropy under psilocybin than at baseline, meaning that a more random sequence of motifs played-out in the psychedelic state. This result implies that it is harder to predict the sequence of connectivity motifs in the psychedelic state because it is more random. This outcome is entirely consistent with the entropic brain hypothesis, which states that brain activity becomes more random and so harder to predict in primary states - of which the psychedelic state is an exemplar.

## CRITICALITY AND PRIMARY CONSCIOUSNESS

The DMN appears to have a consistently high level of activity, e.g., even when the DMN is relatively deactivated during goal-directed cognition, it is still receives more blood flow than elsewhere in the brain (Pfefferbaum et al., 2011). Thus, it can be inferred that one reason why the DMN is so highly and persistently active, is that it receive regular endogenous input from internal drivers. One such driver may be MTL activity (Laxton et al., 2010) and another may be input from brainstem nuclei such as the serotonergic raphe nuclei. Irrespective of what the specific drivers of the DMN are, its enduring presence fits comfortably with the idea that it is the seat of the ego (Carhart-Harris and Friston, 2010), as in healthy waking consciousness, one's sense of self is never far from consciousness:

> "Normally, there is nothing of which we are more certain than the feeling of our self, of our own ego." (Freud, 1930)

So how does the phenomenon of primary consciousness fit in here? The first thing to say is that primary consciousness may be a sub-optimal mode of cognition that has been superseded by a more reality-bound style of thinking, governed by the ego. However, if primary consciousness is a psychological atavism, and the psychedelic state is an exemplar of it, then how does this explain the putative utility of the psychedelic experience e.g., as an adjunct to psychotherapy (Moreno et al., 2006; Grob et al., 2011) and why do some people report being so profoundly affected by such experiences (and often seemingly for the better) (Griffiths et al., 2008; Carhart-Harris and Nutt, 2010; MacLean et al., 2011)?

The phenomenon of depression can help us here. Cognition during an episode of depression is characteristically inflexible; the patient's focus is almost entirely inward and self-critical, and *he/she is unable to remove him/herself from this state* (Holtzheimer and Mayberg, 2011). In the previous section, depressive realism was discussed in relation to hyper activity and connectivity within the DMN; however, in severe depression, cognition cannot be said to be optimal. Depressed patients typically perceive themselves and their world through an unyielding pessimism (Styron, 1992). Depressed patients' cognitive style may become too fixed, such that the patient loses the ability to think and behave in a flexible manner. Underlying this phenomenon may be a decrease in metastability, such that one particular state, e.g., the introspective default-mode, comes to dominate cognition. The aggressive self-critical focus that accompanies a loss or abandonment of object-cathexis in depression (i.e., interest in or focus on objects in the world, such as work and people) quite naturally leads to suicidal thoughts and acts (Carhart-Harris et al., 2008). In consideration of these things, narrow-mindedness is to pessimism what openness (MacLean et al., 2011) is to optimism and strategies that promote the latter may be effective treatments for depression (see MacLean et al., 2011).

This article proposes that primary consciousness rests on more metastable dynamics than secondary consciousness, i.e., brain sub-states are less stable in primary consciousness. Thus, by implication, a broader repertoire of transient states may be visited in primary consciousness because the system is closer to criticality-proper. Moreover, it is the ability of psychedelics to disrupt stereotyped patterns of thought and behavior by disintegrating the patterns of activity upon which they rest that accounts for their therapeutic potential. This principle implies that a brain at criticality may be a "happier" brain. The schematic below (**Figure 7**) illustrates differences between primary and secondary consciousness. The model describes cognition in adult modern humans as "near critical" but "sub-critical"—meaning that its dynamics are poised in a position between the two extremes of formlessness and petrification where there is an optimal balance between order and flexibility. However, because of maturational settling, the brain in secondary consciousness gravitates toward "order" and thus, the dynamics in this state are more accurately, (slightly) sub-critical. Psychedelics may be therapeutic because they work to normalize pathologically sub-critical styles of thought (such as is seen in depression, OCD or addiction/craving for example) thereby returning the brain to a more critical mode of operating. Indeed, if the principle holds that a critical brain is a happy brain, then it would follow that psychedelics could be used to enhance well-being and divergent thinking, even in already healthy individuals. One negative consequence of this however could be the neglect of accurate reality-testing.

Recent work has indeed supported the notion that brain activity is slightly sub-critical in normal waking consciousness (Priesemann et al., 2013). One reason why it may be advantageous for the brain to operate just below criticality is that by doing so, it can exert better control over the rest of the natural world—most of which *is* critical. This may take the form of suppressing endogenous processes within the brain or interacting with the environment in order to shape it and thereby control it. Indeed, if control is the objective, then it makes sense that the brain should be more ordered than that which it wishes to control.

The idea that the brain is closer to criticality in the psychedelic state than in normal waking consciousness (**Figure 7**) has some intuitive appeal as some of the signatures of criticality,

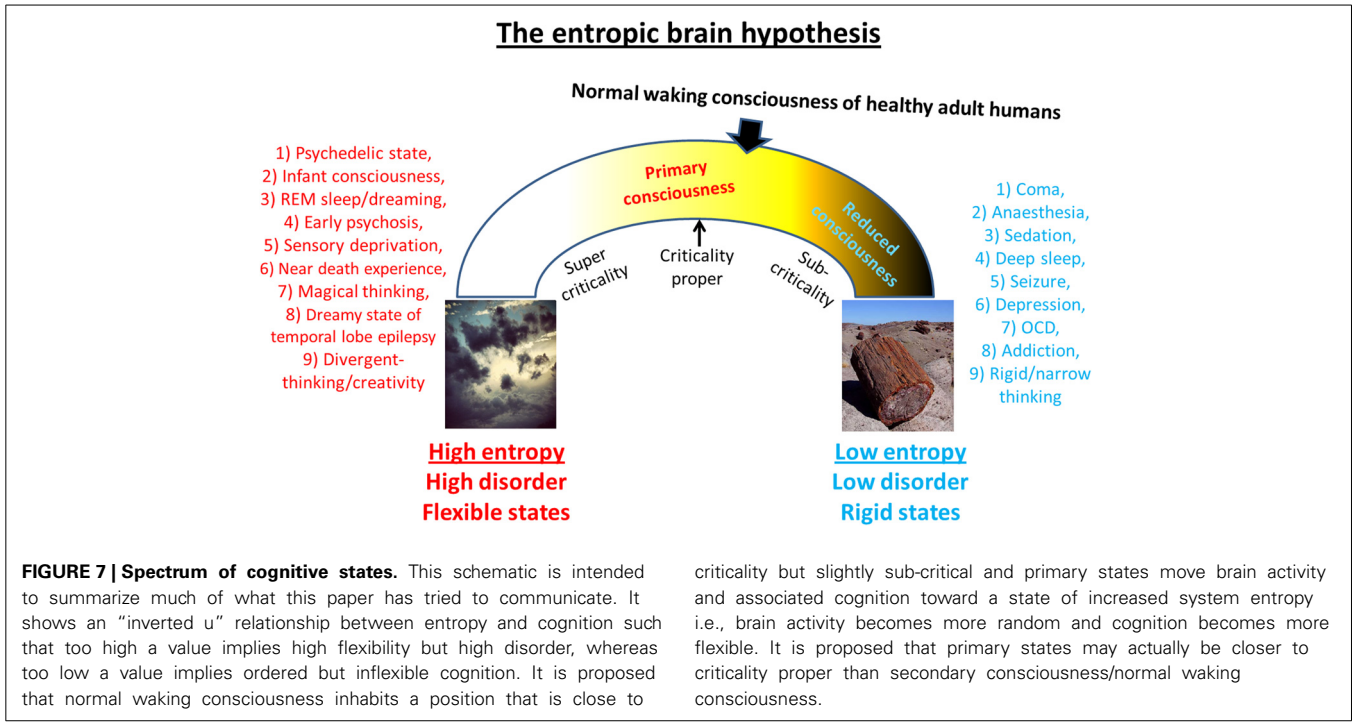


**FIGURE 7 | Spectrum of cognitive states.** This schematic is intended to summarize much of what this paper has tried to communicate. It shows an "inverted u" relationship between entropy and cognition such that too high a value implies high flexibility but high disorder, whereas too low a value implies ordered but inflexible cognition. It is proposed that normal waking consciousness inhabits a position that is close to criticality but slightly sub-critical and primary states move brain activity and associated cognition toward a state of increased system entropy i.e., brain activity becomes more random and cognition becomes more flexible. It is proposed that primary states may actually be closer to criticality proper than secondary consciousness/normal waking consciousness.

such as maximum metastability, avalanche phenomena and hypersensitivity to perturbation are consistent with the phenomenology of the psychedelic state. For example, if we consider just one of these: hypersensitivity to perturbation, it is well known that individuals are hypersensitive to environmental perturbations in the psychedelic state, which is why such emphasis is placed on the importance of managing the environment in which the psychedelic experience unfolds (Johnson et al., 2008). Indeed, one explanation for why some people celebrate and romanticize the psychedelic experience and even consider it "sacred" (Schultes, 1980; McKenna, 1992), is that, in terms of criticality, brain activity does actually become more consistent closer with the rest of nature in this state i.e., it moves closer to criticality-proper and so is more in harmony with the rest of nature.

A final speculation that is worth sharing, is that the claim that psychedelics work to lower repression and facilitate access to the psychoanalytic unconscious, may relate to the brain moving out of a sub-critical mode of functioning and into a critical one, enabling transient windows of segregation or modularity to occur (e.g., with "anarchic" MTL activity) because of the breakdown of the system's hierarchical structure. Indeed, repression may depend on the brain operating in a sub-critical mode, since this would constrain consciousness and limit its breadth. Phenomena such as spontaneous personal insights and the complex imagery that often plays out in psychedelic state (Cohen, 1967) and dreaming, may depend on a suspension of repression, enabling cascade-like processes to propagate through the brain [e.g., from the MTLs to the association cortices (Bartolomei et al., 2012)]. Such processes may depend on a reduction of DMN control over MTL activity.

## THE THERAPEUTIC POTENTIAL OF PSYCHEDELICS

Many psychiatrists working with psychedelics in the 1950s and 60s expressed great enthusiasm about their therapeutic potential (Crocket et al., 1963; Abramson, 1967; Grinspoon and Bakalar, 1979; Grof, 1980) but there was an unfortunate failure to substantiate these beliefs with properly controlled studies. Subsequent reviews and meta-analyses have suggested an impressive efficacy, especially in relation to the use of LSD in the treatment of alcohol dependence (Mangini, 1998; Dyck, 2005; Krebs and Johansen, 2012) and modern trials have lent some support to this sentiment (Moreno et al., 2006; Grob et al., 2011). For example, a single high dose of psilocybin produced profound existential experiences in healthy volunteers that had a lasting beneficial impact on subjective well-being (Griffiths et al., 2006, 2008) and a moderate single dose of psilocybin administered to patients with advanced-stage cancer significantly reduced anxiety and depression scores for months after the acute experience (Grob et al., 2011). In another study, symptoms of obsessive compulsive disorder (OCD) were significantly reduced after psilocybin (Moreno et al., 2006). Supplementing these controlled studies, we surveyed over 500 recreational drug users, and found that 67% of LSD users and 60% of psilocybin users claimed that use of these drugs had produced long-term positive effects on their sense of well-being (Carhart-Harris and Nutt, 2010), consistent with the results of the aforementioned controlled studies (Griffiths et al., 2006, 2011). To place this in a context, only 6% of alcohol users claimed

such improvements from alcohol use (Carhart-Harris and Nutt, 2010). One of the most remarkable properties of psychedelics is their potential to have a lasting impact on personality and outlook (McGlothlin and Arnold, 1971; Studerus et al., 2011). Personality traits are known to be relatively fixed by adulthood (Costa and McCrae, 1997; McCrae and Costa, 1997), however, the personality trait "openness" was found to be significantly increased over 14 months after a single controlled administration of psilocybin (MacLean et al., 2011). Moreover, neuroimaging studies (Carhart-Harris et al., 2012a) have found decreased activity and connectivity after psilocybin in brain regions (e.g., the mPFC) and networks (e.g., the DMN) that are over-engaged in depression (Greicius et al., 2007; Berman et al., 2011) but normalized by a range of effective treatments (Goldapple et al., 2004; Mayberg et al., 2005; Kennedy et al., 2007; Deakin et al., 2008).

Classic psychedelics are all agonists at the serotonin 2A receptor (Glennon et al., 1984; Vollenweider et al., 1998) and 5-$HT_{2A}$R antagonism blocks the positive mood effects of psilocybin (Kometer et al., 2012) and MDMA (van Wel et al., 2012). 5-$HT_{2A}$R expression is upregulated in depression (Bhagwagar et al., 2006) likely because of low synaptic 5-HT (Cahir et al., 2007). Positron emission tomography (PET) studies in humans found positive correlations between 5-$HT_{2A}$R binding and trait neuroticism (Frokjaer et al., 2008) and pessimism (Meyer et al., 2003). This may imply that 5-$HT_{2A}$R upregulation, due to low synaptic 5-HT, reflects a state of chronically deficient post-synaptic 5-$HT_{2A}$R stimulation that contributes to inflexible patterns of (negative) thought such as are seen in depression. 5-$HT_{2A}$R-stimulation may therefore work to reverse this, effectively "lubricating" cognition.

Given our knowledge of the biological effects psychedelics, a comprehensive model can be presented in which psychedelics: (1) stimulate the 5-$HT_{2A}$ receptor (Glennon et al., 1984), (2) depolarize deep-layer pyramidal neurons (Andrade, 2011), (3) desynchronize cortical activity, (4) "disintegrate" brain networks (Carhart-Harris et al., 2012a), (5) increase network metastability and (6) increase the repertoire of connectivity motifs within a limbic/paralimbic network. The net effect of these processes is an increase in system entropy (formally reflected in points 5 and 6) as the system enters criticality-proper.

Thus, in summary, it is hypothesized that there is a basic mechanism by which psychedelics can be helpful in psychiatry, whether they be used to treat depression, OCD (Moreno et al., 2006) or addiction (Krebs and Johansen, 2012). Specifically, it is proposed that psychedelics work by dismantling reinforced patterns of negative thought and behavior by breaking down the stable spatiotemporal patterns of brain activity upon which they rest. An important caveat however, is that in order for this process to be beneficial, the drug-induced transitions to, and the return from primary consciousness, must be mediated by appropriate therapeutic care (Johnson et al., 2008). Moving the brain out of sub-critical modes and into unfamiliar terrain may present some risks (e.g., loss of contact with reality and persistent magical/delusional thinking) if not properly managed (Johnson et al., 2008).

## THE SPIRITUAL EXPERIENCE AND PRIMARY CONSCIOUSNESS

> "If we consider contemporary accounts of the mystical consciousness, we can see that the individuality, the "I," disappears and is in a sense "annihilated." (Stace, 1961)

In the psychology of religion, one of the most remarkable findings has been that it is possible, by way of a single high dose of psilocybin, to reliably induce profound spiritual experiences in healthy volunteers that are effectively indistinguishable from spontaneously-occurring spiritual experiences (Griffiths et al., 2006). Perhaps this finding should not be so surprising, psilocybin containing mushrooms have been used for centuries in shamanic "healing" ceremonies (Hofmann, 1980), and in a famous study in the 1960s, high-dose psilocybin was administered to theology students partaking in a religious service on Good Friday and emphatic spiritual experiences were reported (Doblin, 1991). The so-called "entheogenic" (generating the divine) properties of psilocybin appear to be shared by the other classic psychedelics such as LSD and DMT but not the "psychedelic-like" compounds, MDMA and cannabis (Carhart-Harris and Nutt, 2010; Lyvers and Meester, 2012). It is intriguing that entheogenic properties appear to be specific to 5-$HT_{2A}$R agonist classic psychedelics and this suggests a key role for this receptor in their genesis.

In William James' famous lectures on the psychology of religion he proposed that spiritual experiences depend on the emergence of what he referred to as the "subconscious" or "subliminal" mind into consciousness (James, 1968). Referring to what psychoanalysis calls "the unconscious." James said: "*[T]his is obviously the larger part of each of us, for it is the abode of everything that is latent and the reservoir of everything that passes unrecorded or unobserved... It is the source of our dreams... In it arise whatever mystical experiences we may have... It is also the fountain-head of much that feeds our religion. In persons deep in the religious life—and this is my conclusion—the door into this region seems unusually wide open*." (James, 1968).

James' ideas are consistent with those of Carl Jung; however, Jung extended them, arguing that the unconscious hosts the psychological remnants of our phylogenetic ancestry. In dreams, psychosis and other altered states, archetypal themes shaped by human history emerge into consciousness (Jung, 1982a). Jung's account of the "collective" unconscious fits comfortably with the phenomenology of the psychedelic experience. Archetypal themes feature heavily in user "trip reports" (Masters and Houston, 1966; Shanon, 2002), as they do in religious iconography. For Jung, religion is a manifestation of the collective unconscious, expressed in a symbolic and ritual form: "*The brain is inherited from its ancestors; it is the deposit of the psychic functioning of the whole human race. In the brain, the instincts are preformed, and so are the primordial images which have always been the basis of man's thinking—the whole treasure-house of mythological motifs... Religious symbols have a distinctly "revelatory" character; they are usually spontaneous products of unconscious psychic activity... they have developed, plant-like, as natural manifestations of the human psyche*." (Jung, 1982b).

Jung's ideas offer an appealing explanation for the content of religious experiences, as well as the content of high-dose psychedelic experiences; however, a more systematic treatise on the spiritual experience was provided by Walter Stace in 1960 (Stace, 1961). Stace's work is particularly useful because his ideas resonate with the findings of recent neuroimaging studies relevant to the neurobiology of spiritual experiences. Based on a thorough review of first-person accounts derived from individuals from a variety of different faiths, Stace identified seven universal components of the spiritual experience: 1) diminished spatial and temporal awareness, 2) diminished subjectivity (equivalent to increased objectivity), 3) feelings of profound joy and peace, 4) a sense of divinity, 5) paradoxicality (where two opposing things appear to be true), 6) ineffability (the difficulty of expressing the experience in words) and 7) a sense of oneness with the world, otherwise known as "the unitive experience."

Importantly, in Stace's synopsis, he identified the unitive experience as the core characteristic of the spiritual experience. Freud referred to the same phenomenon as the "oceanic state" (Freud, 1930). Stace explained that in profound spiritual experiences the complex *multiplicity* of normal consciousness collapses into a simpler state where a sense of an all-encompassing unity or "oneness" with others, the world and/or "God" is felt. He emphasized that there is a collapse in the most fundamental dualities of consciousness (i.e., *self* vs. *other*, *subject* vs. *object* and *internal* vs. *external*) in the unitive state. Moreover, he also showed that reports of unitary consciousness are consistent throughout the different religions—emphasizing its universality and cultural independence (Stace, 1961).

Freud had some important things to say about the unitive state that are directly relevant to the entropic brain hypothesis. For example, when discussing his friend's description of an "oceanic feeling" when in religious practice, Freud says: "*Pathology has made us acquainted with a great number of states in which the boundary lines between the ego and the external world become uncertain... Further reflection tells us that the adult's ego-feeling cannot have been the same from the beginning. It must have gone through a process of development... (For example,) an infant at the breast does not as yet distinguish his ego from the external world; he gradually learns to do so. Our present ego-feeling is therefore only a shrunken residue of a much more inclusive—indeed, an all-embracing feeling, which (early in development] corresponded to a more intimate bond between the ego and the world. If we assume that there are many people in whose mental life this primary ego-feeling has persisted to a greater or less degree, it would exist in them side by side with the narrower and more sharply demarcated ego feeling of maturity, like a counterpart to it. In that case, the ideational contents appropriate to it would be precisely those of limitlessness and of a bond with the universe—the same ideas with which my friend elucidated the "oceanic feeling.*"" (Freud, 1930).

Thus, Stace and Freud's descriptions of the spiritual experience are entirely consistent with the view of the primary state as being regressive. Moreover, they are also consistent with view that the human brain developed through ontogeny and phylogeny to minimize disorder/uncertainty (Friston, 2010). In the schematic presented in **Figure 7**, primary consciousness is depicted as being more supercritical than normal waking consciousness. Indeed, at the extreme end of supercriticality is maximum entropy, which is equivalent to formlessness or complete disorder. Formerly, there is no difference between entropy in this thermodynamic sense (depicted as complete disorder) and entropy in the information theory sense, where there is maximum uncertainty about the system - because there is no order on which to base any predictions.

## THE SYSTEM MECHANICS OF PRIMARY STATES

Extending this, the mechanics underlying the onset of true primary states (for which the spiritual experiences is an example) can be viewed in relation to the second law of thermodynamics. Explicitly, in the absence of a regular driving input, the system (i.e., self-organized brain activity) will inevitably degrade or collapse toward formlessness or maximum entropy. The interesting question that follows therefore is: *what is the driving input that ceases in primary states*? This paper proposes that regular MTL activity is a crucial driver of the DMN. Although, interestingly, there is also evidence that the usual clock-like firing of serotonin neurons in the dorsal raphe nuclei completely ceases in both the psychedelic state (Aghajanian et al., 1968; Aghajanian and Vandermaelen, 1982) and REM sleep (Trulson and Jacobs, 1979) and there is some indirect evidence that the DMN may be (at least partially) a serotonergic system coupled to dorsal raphe activity (Zhou et al., 2010).

During secondary consciousness, the brain can enter a *multiplicity* of different states and microstates (Tononi, 2010) but due to "winner-takes all," or more strictly, "winnerless" (Rabinovich et al., 2001) competition between states ["winnerless" because critical instability or metastability dictates that a state's "victory" is transient (Friston et al., 2012b)] the global system only ever entertains *one* winning state at any one time (Baars, 2005). However, according to the entropic brain hypothesis, in primary states, the potential multiplicity of possible states is not obliterated but rather extended because the *selectivity* and *conspicuity* of a winning state is reduced, and so more transient states may be visited. In dynamical terms, this would be expressed as attractor basins or valleys (defining transient states) becoming shallower in primary states, i.e., the attractor landscape is flattened in primary states.

Conversely, in depression, OCD and addiction, specific states (e.g., the default-mode in depression) may be frequented more regularly than others—and this may be observed as certain mental states (e.g., introspection in depression or craving in addiction) or behaviors (e.g., compulsive acts in OCD) being habitually revisited in a stereotyped fashion. Moreover, these states may be relatively stable i.e., their basins of attraction are relatively steep since the patterns of activity upon which they rest have become entrenched. In such scenarios, uncertainty about the system is minimized because we know that it possesses a particular character. It is intriguing to consider therefore that disorders such as depression, OCD and addiction could be functional in some sense, perhaps working to resist a more catastrophic collapse to primary consciousness (with the onset of a psychotic episode for example) by reinforcing stable patterns of activity.

The following example may help to illustrate what is meant by competition between conscious states—and the loss of it in primary consciousness. Functional brain imaging has identified

distinct brain networks that subserve distinct psychological functions. For example, the DMN is associated with introspective thought (Andrews-Hanna et al., 2010) and a dorsal frontoparietal attention network (DAN) is associated with visuospatial attention (Corbetta et al., 1998; Fox et al., 2006) and is a classic example of a "task positive network" (TPN)—i.e., a network of regions that are consistently activated during goal-directed cognition. If the brain was to be sampled during a primary state (such as a psychedelic state) we would predict that the rules that normally apply to normal waking consciousness will become less robust. Indeed, we recently found this to be so when analysing the degree of orthogonality or "anti-correlation" between the DMN and TPN post-psilocybin. Post-drug there was a significant reduction in the DMN-TPN anticorrelation, consistent with these networks becoming less different or more similar (i.e., a flattening of the attractor landscape). The same decrease in DMN-TPN anticorrelation has been found in experienced meditators during rest (Brewer et al., 2011) and meditation (Froeliger et al., 2012). Moreover, decreased DMN-TPN inverse coupling is especially marked during a particular style of meditation referred to as "non-dual awareness" (Josipovic et al., 2011). This is interesting because this style of meditation promotes the same collapse of dualities that was identified by Stace (and Freud) as constituting the core of the spiritual experience. The DMN is closely associated with self-reflection, subjectivity and introspection, and task positive networks are associated with the inverse of these things, i.e., focus-on and scrutiny of the external world (Raichle et al., 2001). Thus, it follows that DMN and TPN activity *must* be competitive or orthogonal in order to avoid confusion over what constitutes *self*, *subject* and *internal* on the one hand, and *other*, *object* and *external* on the other. It is important to highlight that disturbance in one's sense of self, and particularly one's sense of existing apart from one's environment, is a hallmark of the spiritual (Stace, 1961) and psychedelic experience (Carhart-Harris et al., 2012b). Moreover, as in the psychedelic state (Carhart-Harris et al., 2012a; Carhart-Harris et al., 2012b), a number of studies have found decreased DMN activity (Farb et al., 2007; Brewer et al., 2011; Hasenkamp et al., 2012) as well as decreased DMN-TPN inverse coupling in meditation (Brewer et al., 2011; Josipovic et al., 2011; Froeliger et al., 2012).

The contravention or corruption of important rules about brain organization may explain the sense of confusion and uncertainty that accompanies a transition from secondary to primary consciousness. In the information theoretical sense, "uncertainty" is a synonym for entropy (Friston, 2010; Ben-Naim, 2012)—and disorder and uncertainty are effectively equivalents. Entropy in information theory is reflected in the shape of a probability distribution (Ben-Naim, 2012), i.e., we have less confidence (or more uncertainty) about something when the distribution is broader or more evenly spread. This is because it is more difficult to predict what the outcome of an individual sampling trial would be because the system behaves relatively randomly (Ben-Naim, 2012). Conversely, a probability distribution with a sharp peak would reflect a well-ordered system or high-precision, confidence or assuredness (Friston, 2010). In the specific context of the DMN and the psychedelic state, just as there is increased variance in parameters defining the DMN (e.g., coupling between the nodes of the DMN or rhythmic alpha oscillations in the PCC), so there is uncertainty about ones sense of self—typically described as "ego-disintegration." Thus, according to the entropic brain hypothesis, just as normally robust principles about the brain lose definition in primary states, so confidence is lost in "how the world is" and "who one is" as a personality.

In addition to the word "uncertainty," other terms that have been used as synonyms for entropy include: "freedom," "disorder" and "expansion." The example of a gas expanding post release of constraints is often used as a metaphor to help explain what is meant by entropy increasing [e.g., in relation to the second law of thermodynamics (Ben-Naim, 2012)] See **Figure 8**. In the information theoretical sense, entropy/uncertainty increases as the gas expands because with greater expansion, it is more difficult to predict the spatial location of a single molecule. It is probably not coincidental that these physical principles resonate with popular descriptions of the psychedelic experience (Huxley, 1959; Bowers and Freedman, 1966; Masters and Houston, 1972; Grinspoon and Bakalar, 1981; Merkur, 1998). For example, the term "consciousness-expansion" is often used to describe the psychedelic experience—and this may be an inadvertent reference to increased system entropy in the psychedelic state.

## DEVELOPING THE CONSTRUCT VALIDITY OF PRIMARY CONSCIOUSNESS

To develop the construct validity of primary consciousness, it will be necessary to show that the identified parameters of primary

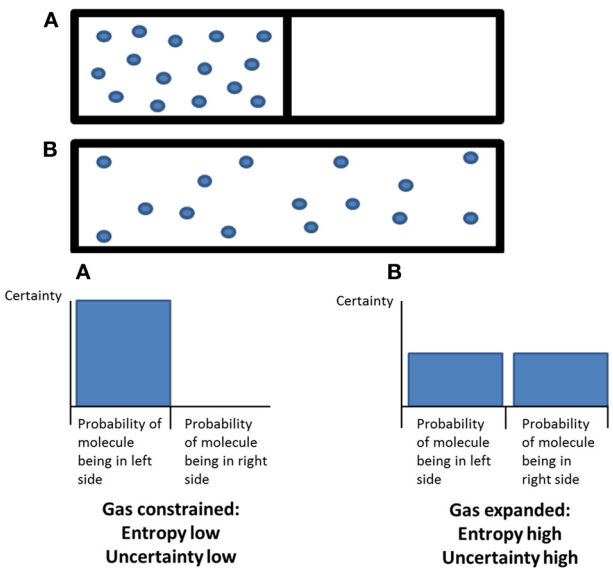


**FIGURE 8 | Gas expansion post-release of constraints as a metaphor for increased entropy in primary states. (A)** Entropy is low while the gas is constrained. **(B)** Entropy increases once constraints are released. In an information theoretical sense, entropy/uncertainty is increased post-expansion because it is more difficult to predict the spatial location of a single molecule. In primary vs. secondary states, it is hypothesized that the biological parameters known to define key brain states (e.g., the default-mode) become more variant or less predictable, thus causing the subject to become less certain in themselves and their experience of the world.

consciousness have high *internal* and *convergent* validity (i.e., properties of primary consciousness must be shown to exist in a range of different primary states) and sufficient *discriminant* validity (i.e., these properties must be shown to be sufficiently *specific* to primary states, i.e., to be absent in non-primary states). To assist this undertaking, it will be important to optimize subjective rating scales designed for assessing primary consciousness. For example, first it will be necessary to identify key experiences that are considered characteristic of primary states (i.e., visual analog scale items such as "my imagination was extremely vivid" or "the experience had a dreamlike quality" that can be rated during or after a candidate primary state) and then it will be important to test whether different candidate primary states (e.g., dreaming, onset-phase psychosis, the near death experience, the sensory-deprived state and the psychedelic drug state) score highly on these items—and that candidate non-primary states (e.g., normal waking consciousness, the anaesthetized or sedated state, and the depressed state) do not. This will enable the convergent and discriminant validity of these measures to be tested and developed. Similarly, by identifying neurobiological characteristics hypothesized to be essential to primary states (e.g., decreased DMN-MTL coupling, disinhibited MTL activity, decreased DMN-TPN anti-correlation, decreased alpha power in the PCC and increased metastability in resting-state networks), it will be important to determine those that most *reliably* and *specifically* identify primary over non-primary states.

As discussed in The research value of psychedelics, psychedelic drugs are especially useful tools for studying primary states as they allow for primary consciousness to be "switched on" with a relatively high degree of experimental control (e.g., with intravenous infusion of a classic psychedelic). Hypotheses about the neurobiological character of primary states can therefore be effectively tested by psychedelic drugs. However, in order to test and develop the generalizability of these hypotheses, research with alternative primary states are required. For example, it would be interesting to carry out simultaneous fMRI-EEG or MEG work with a focus on REM sleep, or to study patients exhibiting early-phase psychotic symptoms with these techniques. Longitudinal analyses looking at brain maturation would also be relevant, where infant consciousness is hypothesized to be reflective of primary consciousness.

## DEVELOPING THE CONSTRUCT VALIDITY OF SECONDARY CONSCIOUSNESS AND THE EGO

As outlined above, a key distinction between the primary and secondary modes of cognition is that secondary consciousness pays deference to reality and diligently seeks to represent the world as *precisely* as possible, whereas primary consciousness is less firmly anchored to reality and is easily misled by simple explanations motivated by wishes and fears. One way this distinction could be tested would be to utilize a measure of metacognitive accuracy (Fleming et al., 2010). As outlined above, metacognition, and specifically the ability to reflect upon one's own introspection, is a particularly advanced behavior associated with the DMN (Fleming et al., 2010). For example, a behavioral paradigm could be designed that requires a participant's friend to rate the participant's personality, e.g., using a standard personality inventory. Then, during scanning, the participant could be asked to predict their friend's ratings—and crucially, to provide an additional confidence rating for their own predictions. This could be done under a psychedelic drug and under placebo in a within-subjects design with 2 different friends for each condition, counterbalanced for key factors (e.g., familiarity, intimacy, fondness, duration of relationship etc). This task would provide a behavioral index of a high-level metacognitive function associated with the ego (theory-of-mind). The hypothesis would be that participants would be *less confident* in their predictions of their friend's ratings post-psilocybin and that the accuracy of their predictions would also be compromised. Biologically, one would hypothesize decreased within-DMN coupling during the prediction process and a reduction in induced alpha-oscillations in the PCC.

## CONCLUSIONS

This article has argued that scientific research with psychedelic drugs can have a revitalizing effect on psychoanalysis and an informing influence on mainstream psychology and psychiatry. Rather than discuss the content and interpretation of psychoanalytically-relevant material, we have adopted a mechanistic approach, in keeping with the mainstream cognitive neuroscience. This article proposes that a distinction can be made between two fundamentally different modes of cognition: primary and secondary consciousness. Primary consciousness is associated with unconstrained cognition and less ordered (higher-entropy) neurodynamics, whereas secondary consciousness is associated with constrained cognition and more ordered neurodynamics (i.e., that strikes an evolutionarily advantageous balance between order and disorder - that may or more not be perfectly "critical"). It is hoped that this mechanistic model will help catalyze a synthesis between psychoanalytic theory and cognitive neuroscience that can be mutually beneficial to both disciplines.

It is a fair criticism of this paper that it has given insufficient consideration to the phenomenological content of the relevant altered states of consciousness, and to the specifics of Freudian theory, and so by neglecting this, has failed to present a sufficiently compelling case that these states have anything to do with psychoanalytic theory. To some extent, this charge can be conceded; however, as outlined in the introduction, the intention of this paper was to develop a mechanistic account of altered states of consciousness based on the quantity of entropy, and this task has demanded a substantial amount of space. A more thorough discussion of the phenomenology of primary states is required to develop the case that they show characteristics that are consistent with Freudian accounts of "the unconscious" or "Id." The reader should be made aware however, that this has been attempted before (Carhart-Harris, 2007; Carhart-Harris and Friston, 2010).

To conclude, it is perhaps not surprising that with only dreaming and psychosis at its disposal, psychoanalysis has failed to convince the scientific community that the psychoanalytic unconscious exists (Hassin et al., 2005). From a neuroscientific perspective, dreaming and psychosis are notoriously difficult to study. The occurrence of dreaming in sleep impedes experimental control and psychosis is an especially complex and variegated phenomenon. However, for those brave enough to embrace it,

research with psychedelics could herald the beginning of a new scientifically informed-psychoanalysis that has the potential to influence modern psychology and psychiatry. The unique scientific value of psychedelics rests in their capacity to make consciously accessible that which is latent in the mind. This paper takes the position that mainstream psychology and psychiatry have underappreciated the depth of the human mind by neglecting schools of thought that posit the existence an unconscious mind. Indeed, psychedelics' greatest value may be as a remedy for ignorance of the unconscious mind.

> "He who would fathom the psyche must not confuse it with consciousness, else he veils from his own sight the object he wishes to explore." (Jung, 1961)

> "Man's worst sin is unconsciousness." (Jung, 1969)

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# Are microglia minding us? Digging up the unconscious mind-brain relationship from a neuropsychoanalytic approach

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The unconscious mind-brain relationship remains unresolved. From the perspective of neuroscience, neuronal networks including synapses have been dominantly believed to play crucial roles in human mental activities, while glial contribution to mental activities has long been ignored. Recently, it has been suggested that microglia, glial cells with immunological/inflammatory functions, play important roles in psychiatric disorders. Newly revealed microglial roles, such as constant direct contact with synapses even in the normal brain, have defied the common traditional belief that microglia do not contribute to neuronal networks. Recent human neuroeconomic investigations with healthy volunteers using minocycline, an antibiotic with inhibitory effects on microglial activation, suggest that microglia may unconsciously modulate human social behaviors as "noise." We herein propose a novel unconscious mind structural system in the brain centering on microglia from a neuropsychoanalytic approach. At least to some extent, microglial activation in the brain may activate unconscious drives as "psychological immune memory/reaction" in the mind, and result in various emotions, traumatic reactions, psychiatric symptoms including suicidal behaviors, and (psychoanalytic) transference during interpersonal relationships. Microglia have the potential to bridge the huge gap between neuroscience, biological psychiatry, psychology and psychoanalysis as a key player to connect the conscious and the unconscious world.

**Keywords: microglia, psychoanalysis, emotion, stress, unconscious, death instinct, suicide, psychiatry**

## INTRODUCTION

> "We have often heard it maintained that sciences should be built up on clear and sharply defined basic concepts. In actual fact no science, not even the most exact, begins with such definitions. The true beginning of scientific activity consists rather in describing phenomena and then in proceeding to group, classify and correlate them. Even at the stage of description it is not possible to avoid applying certain abstract ideas to the material in hand, ideas derived from somewhere or other but certainly not from the new observations alone. Such ideas—which will later become the basic concepts of the science—are still more indispensable as the material is further worked over (Freud, 1915)" (Instincts and their Vicissitudes. 1915).

Sigmund Freud established psychoanalysis, which continued to develop and spread worldwide within and outside psychiatry until the 1970s. At the same time, neuroscience and biological psychiatry have followed their own developmental paths. Psychopharmacological treatments had become widely accepted for mental illness since the 1970s and by the 1980s, psychoanalysis was regarded to be outdated, even unscientific (Wolpert and Fonagy, 2009; Fonagy and Lemma, 2012; Salkovskis and Wolpert, 2012). However with the rethinking of Freudian concepts, neuroscience has recently started to refocus upon psychoanalytic theories in the novel field of neuropsychoanalysis (Fonagy, 2001; Solms and Lechevalier, 2002; Solms and Turnbull, 2002; Panksepp, 2007; Arminjon et al., 2010; Northoff, 2011; Panksepp and Solms, 2012).

As a matter of fact, Freud himself began his career as a neurologist, and was a leading neuroscientist in the late 19th century before his establishment of psychoanalysis. His neuronal network idea at that time can actually be found in his private letters to Wilhelm Fliess. Charles Scott Sherrington, a famous British physiologist, discovered gaps between neurons and called them "synapses" in 1887. Two years before the Sherrington's discovery, Freud sketched synapse-like drawings and the existence of a energy source in his private letter (**Figure 1**) (Freud, 1950 [1895]). This fact highlights Freud's foresight in neuroscience. However, after he had established psychoanalysis, he devoted himself to developing not neuroscientific but psychological theories, and never published his schemes of neurons during his life (Northoff, 2012). Could it be possible that Freud might have dreamed of biological explanations of the mind that would one day replace psychological ones? If he had lived in our modern era, he might have proposed such a hypothesis to modern neuroscientists.

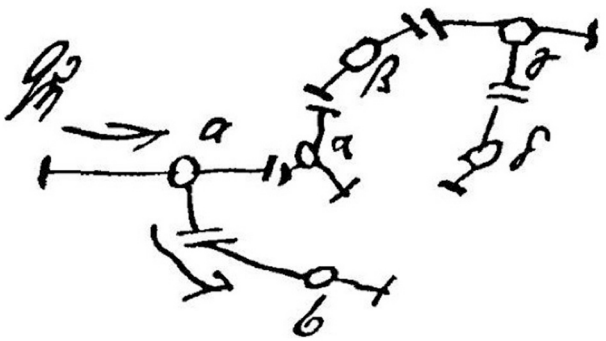

**FIGURE 1 | Freud's sketch of the neuronal mechanism of the mind.** Freud proposed a neuronal mechanism of repression in 1895. This is the famous sketch of his idea. He forecasted the existence of the "synapse" in this sketch. According to his scheme of unpleasant memory, a stimulus (Qη) normally activates unpleasant memory from neuron "a" to neuron "b"; however if other neurons ("α" and "β") exert a "repressing" influence, such activation is prevented. Based on our microglia theory, the function of "Qη" and/or "α" could be equivalent to a function of microglia as an energy source. Not only "repression" but also other unconscious functions, which were discovered by Freud and later psychoanalysts, may be modulated by microglia.

## IS THE MIND A COMPUTER? DO COMPUTERS NEED ENERGETIC DRIVES?

Various hypotheses have been investigated to clarify the relationship between the mind and the brain; however the underlying mechanism remains unresolved. Traditionally, from a neuroscience perspective, the mind has been regarded to consist of neurons and neuronal circuit systems including synapses in the brain in the same way that computers consist of intricate metallic circuitry, and this view has persisted to the present day. In addition, the pathophysiology of mental illness has also been regarded to be within the context of neuronal circuit disturbances via neurotransmitters. On the other hand, a century ago, Freud proposed an energy model of the unconscious mind initially described as "Qη" (**Figure 1**) (Freud, 1950 [1895]), although this idea has been greatly ignored within the neuroscientific world. However, the computer itself does not work without energy and will only work adequately when the energy systems, such as heating/cooling, operate appropriately. Similar to a computer system model, additional energy systems in the brain may be needed to operate the mind. Originally, Freud and psychoanalytic researchers conceptualized "energy" similar to the thermodynamic conception of energy that all energy tends to ultimate equalization and stabilization and that, therefore, units of higher energy content within a system of lower energy content are unstable and tend to degrade, by importing physics theories from metapsychological perspectives (Freud, 1895, 1933a; Bernfeld and Feitelberg, 1931; Penrose, 1931; Erdelyi, 1985). On the other hand, recent biological studies have suggested that inflammation and oxidative stress, two of the most important energies in the brain, play important roles in the pathophysiology and interventions of various mental illnesses (Ng et al., 2008; Kato et al., 2011a; Maes et al., 2011, 2012). Herein, we propose a novel theory of an unconscious mind structural system in the brain by importing the role of microglia as the energy source and modulator of the brain from a neuropsychoanalytic approach (Solms and Lechevalier, 2002; Solms and Turnbull, 2002; Panksepp, 2007; Northoff, 2011; Panksepp and Solms, 2012).

## WHAT ARE MICROGLIA?

Microglia, which were initially discovered by del Rio Hortega in 1919, are one of the glial cells in the brain. Traditionally, neuroscientists regarded microglial function as simply providing physical support and maintenance for neurons. Thus, in this limited role microglia had been long ignored (Miller, 2005). The last 20 years have elucidated various biological functions of microglia that act as "brain macrophage"; crucial immunological/inflammatory players in the brain by moving around and releasing cytokines and free radicals (Block et al., 2007; Hanisch and Kettenmann, 2007). Thus, microglia have proved to play more important roles in normal brain functions and various brain pathologies such as neurodegenerative diseases and neuropathic pain via inducing inflammation and oxidative stress (Inoue and Tsuda, 2009; Graeber, 2010; Graeber and Streit, 2010; Kettenmann et al., 2011; Ransohoff and Stevens, 2011).

## PSYCHIATRIC DISORDERS AND MICROGLIA

Inflammation, oxidative stress, and immunological abnormality have been highlighted in various psychiatric disorders (Ng et al., 2008; Pasco et al., 2010; Kato et al., 2011a; Maes et al., 2011, 2012; Davison, 2012; Nicholson et al., 2012). The pathophysiology of psychiatric disorders has been dominantly believed to be solely explained by abnormalities of neurotransmitter systems. While, recent brain imaging and histological studies have indicated microglial activation in the brain of people with psychiatric disorders such as schizophrenia, depression, and autism (Radewicz et al., 2000; Steiner et al., 2008; Van Berckel et al., 2008; Doorduin et al., 2009; Morgan et al., 2010; Takano et al., 2010). Psychotropic drugs have long been regarded to have effects solely on neurons and neuronal networks including synapses, while our rodent *in vitro* studies have proved the novel effect of psychotropic drugs directly on microglia by suppressing release of inflammatory cytokines and free radicals (Kato et al., 2007, 2008, 2011a,b; Horikawa et al., 2010). Based on the above-mentioned findings, we have proposed a microglial contribution to psychiatric disorders (Monji et al., 2009; Kato et al., 2011a). Immunological/inflammatory activators such as lipopolysaccharide (LPS) and interferon-γ, which are induced by infections, and various stressful life events, may activate microglia in the brain. Activated microglia release proinflammatory cytokines and free radicals (Block and Hong, 2005). In the brain of patients with psychiatric disorders, these mediators may cause brain pathologies such as neuronal degeneration, white matter abnormalities, and decreased neurogenesis (Uranova et al., 2004, 2007; Jarskog et al., 2005; Lieberman et al., 2005; Girgis et al., 2006; Glantz et al., 2006; Macritchie et al., 2010). Such remodelings of neuron-microglia interactions may thus be important factors in the pathophysiology of psychiatric disorders (Monji et al., 2009, 2011; Kato et al., 2011a).

## STRESS, SUICIDE, AND MICROGLIA

Furthermore, recent animal studies indicate that microglia are activated not only under inflammation but also under physical stress (Frank et al., 2007; Sugama et al., 2007, 2009) and under psychosocial stress such as social isolation (Schiavone et al., 2009), chronic restraint stress (Tynan et al., 2010; Hinwood et al., 2012a,b) and social defeated situations (Wohleb et al., 2011). These data suggest that microglia may contribute not only to physical disturbance but also to emotional disturbance. Human postmortem studies have revealed microglial activation in the brain of suicide victims (Steiner et al., 2006, 2008). Suicide has generally been regarded as a byproduct of emotional disturbance, and furthermore, in the field of psychology and psychoanalysis, suicide has been considered to be the result of maladaptive unconscious drives. Herein, the question arises: Could microglia drive our unconscious drives? Before presenting a bridging theory between microglia and unconscious drives, we introduce the historical concept of these psychoanalytic drives.

## THE CONCEPT OF PSYCHOANALYTIC UNCONSCIOUS DRIVES

A century ago, Freud proposed the conception of mind structure models consisting of the following three components: *the id* (unconscious/instinctual drives), *the ego* (the exclusive apparatus of the conscious mind), and *the super ego* (which represses *the id* in order to avoid any disruptions of rational thought). In the process of clarifying the unconscious components—*the id* and *the super ego*, Freud additionally developed the economic energy models of the following unconscious drives; first the "*life instinct (Lebenstrieb)*"—the tendency toward survival, propagation, and other creative life-producing drives, and later the "*death drive (Todestrieb)*" described in "*Beyond the Pleasure Principle* (Freud, 1920)" as "*. . . everything living dies for internal reasons—becomes inorganic once again—then we shall be compelled to say that 'the aim of all life is death' and, looking backwards, that 'inanimate things existed before living ones*'".

Following Freud's discovery of *the death drive*, it has continued to be one of the key concepts of psychoanalysis, which is often considered to form the basis of various emotions/behaviors—anxiety, fear, aggression and envy, and problematic behaviors including violence and suicide (Freud, 1933b; Klein, 1957). Historically, Freud underpinned *the death drive* from clinical phenomena such as negative therapeutic reactions, repetition-compulsion, anxiety dreams in persons with war neurosis, and masochism. Freud considered that *the life instinct* and *the death drive* fuse together in early life stages, and emphasized that *the death drive* was silently driving individuals toward death and that only through the activity of *the life instinct* was this death-like force projected outwards and appeared as destructive impulses directed against objects in the outside world (Freud, 1924). Freud named the outward-directed death drive "the destructive instinct (drive)." Melanie Klein and Karl Menninger were among the very few psychoanalysts who succeeded and developed the concept of *the death drive*. Klein, the Vienna-born British female psychoanalyst, who further developed Freud's concept of *the death drive* and was the basis of the Kleinian school in her later life, regarded the super ego in early life stages as the clinical expression of *the death drive* (Klein, 1932). Based on her theory, humans genetically and potentially have both *the life instinct* (desires for affection and/or objects) and *the death drive* (destructiveness and aggression), and these drives are expressed as internal/external object relations (good object/bad object) (Klein, 1957). Klein and Hanna Segal, a prominent Kleinian psychoanalyst, linked *the death drive* to envy (Segal, 1952, 1993). Segal also linked it to aesthetics by describing that "*Re-stated in terms of instincts, ugliness—destruction—is the expression of the death instinct; beauty—the desire to unite into rhythms and wholes, is that of the life instinct. The achievement of the artist is in giving the fullest expression to the conflict and the union between those two* (Segal, 1952)." Herbert Rosenfeld regarded the death drive in line with the concept of the *pathological organization* (*narcissistic organization*) in which good objects are abolished and destroyed internally in the self (Rosenfeld, 1971). As stated above, Kleinian theory has been continuously developed based on two opposing internal objects; the good object and the bad object. On the other hand, independent group psychoanalysts have developed their own theories. Ronald Fairbairn avoided the good/bad dichotomy, and established a unique object-relation theory with two essential objects; the exciting object and the rejecting object (Fairbairn, 1952). He assumed that the two internal objects were the roots of human behaviors and emotional life. Donald Winnicott emphasized the importance of external objects (environmental factors) in addition to internal objects (Winnicott, 1953, 1960).

Researchers such as Heinz Hartmann, Otto Kernberg, and Jaak Panksepp have fundamentally discussed the concept of instincts and drives in psychoanalysis in connection with biology and affective neuroscience. Hartmann, one of the founders of ego psychology, developed the theory of aggression based on *the death drive* (Hartmann, 1939). In addition, Panksepp, who coined the term "affective neuroscience," has been proposing a provocative theory linking drives and emotions. Based on his neurobiological and neuropsychoanalytic background, he and his colleagues have recently developed the theory of the SEEKING system (Wright and Panksepp, 2012). The SEEKING system is described as a "primary process" that promotes psychomotor eagerness to obtain pleasure generating resources and eliminate calamities, providing euphoric anticipatory excitement, and linking with other drives, such as those apart of the rewarding affective systems of LUST, CARING, and PLAY, and at times the aversive affective systems of FEAR and RAGE (Wright and Panksepp, 2012). Interestingly, in the commentary of the article of Wright and Panksepp, and Kernberg suggested "the concept of 'death drive' be retained for the pathological predominance in some clinical conditions of negative internalized object relations that may lead to an overwhelming dominance of self-destructive motivation (Kernberg, 2012)."

In psychoanalysis, the relationship between Es (id), libido and drive (instinct) has been ambiguously classified. While valuing Freud's original concept of the two essential drives and the following psychoanalytic theories, we believe that these concepts should be modified with accordance to recent theoretical/biological developments as discussed above. In the present day, the majority of psychoanalysts and scholars such as ethologists and

experimental psychologists are skeptical regarding the validity of *the death drive* as a relevant concept (Dufresne, 2000), but many researchers continue to accept the concept of the (aggressive) destructive drive (Rosenfeld, 1971; Feldman, 2000; Britton, 2003; Kernberg, 2012). In this article, we use the term of *the death drive* basically as the destructive drive (instinct), which induces negative emotions and outward destructive behaviors. In the following part, we propose a novel integrating theory of unconscious drives in order to fit both psychoanalytical and biological models.

## BRIDGING THEORY BETWEEN MICROGLIA AND UNCONSCIOUS DRIVES—DO MICROGLIA DRIVE HUMAN MENTAL ACTIVITIES AS THE ORIGIN OF UNCONSCIOUS DRIVES?

To our knowledge, the internal reasons of the death drive have never been clarified from a molecular neuroscientific perspective. We herein propose a novel challenge to dig up the underlying mechanism of the drives with the modern understandings of microglia and their immunological roles in the brain. Obviously, Freud would not have known of such cells, however surprisingly, he implied a linkage between immunity and suicide in the following sentence:

> "…It is noteworthy that the obsessional neurotic, in contrast to the melancholic, never in fact takes the step of self-destruction; it is as though he were *immune* against the danger of *suicide*, and he is far better protected from it than the hysteric (Freud, 1920)."

In the present day, the role of microglia has been understood with a greater clarity than in Freud's era. Synaptic reactions have for a long time been regarded to play an essential role in human mental activities, while only neurons have been highlighted. Now, rodent microglia have proved to contribute to brain development such as synaptic pruning (Paolicelli et al., 2011), which suggest that microglia may play an important role in the process of brain development. Other animal studies have shown that microglia monitor synaptic reactions via direct-touching even in the normal brain (Wake et al., 2009; Graeber, 2010; Ransohoff and Stevens, 2011). Interestingly, some synapses in the ischemic areas disappear after a prolonged microglial contact (Wake et al., 2009), which may suggest that severe mental stress induces synaptic changes via microglial responses. Recent rodent studies have reported that severe stresses including psychosocial stress activate microglia (Frank et al., 2007; Schiavone et al., 2009; Sugama et al., 2009; Tynan et al., 2010; Wohleb et al., 2011; Hinwood et al., 2012a,b). In addition, human studies suggest that microglial activation is observed in the brain of psychiatric patients and suicide victims (Steiner et al., 2006, 2008; Van Berckel et al., 2008; Doorduin et al., 2009; Takano et al., 2010). Under these microglia-activated states, unconscious drives could be highly activated from a psychoanalytic perspective.

In sum, a novel hypothetical theory arises: "When microglia is maladaptively activated in the brain, microglia may act as the origin of unconscious drives such as *the death drive* in the unconscious mind, and induce emotional reactions such as anxiety, fear, aggression, envy, and suicidal thought/behaviors (**Figure 2**)."

## TRANSFERENCE, PSYCHOLOGICAL IMMUNE MEMORY/REACTION, AND MICROGLIA

One of the essential lessons of psychoanalysis represented by the Oedipus complex is that psychological experiences during childhood between people closely related (i.e., mother, father and siblings) last until adulthood, (Freud, 1900, 1905). Unconscious reactions, which are memorized during childhood, are reflected onto immediate persons in various settings such as home, school, and work. These unconscious reactions occurring toward psychoanalysts are called transference; e.g., a client felt enraged toward his psychoanalyst, as he would have experienced toward his father in childhood. Dealing with transference is a major therapeutic approach of psychoanalysis. Psychoanalysts would interpret that his unconscious aggressive drive produced by the father–child relationship is reproduced during the here and now psychoanalyst-client relationship. Owing to such an approach, the client may recognize his own unconsciously derived aggression and he may be released from it.

Transference and its underlying mechanisms can be explained within the paradigm of microglial priming. Bilbo and Schwarz suggest that microglial activation due to infections during early developmental periods last, and these pre-activated microglia will be re-activated rapidly compared to normal state microglia as microglial immune memory (Bilbo and Schwarz, 2009). Interestingly, Bilbo and her colleagues recently reported that early life stress in the rat influence formation of memories in later life by microglial immune memory (Williamson et al., 2011).

Various stressors, not only infection but also psychosocial stress, may be memorized inside the microglia during childhood as the origin of unconscious drives, which we have dubbed "psychological immune memory." In later life, various similar stressors re-activate the microglia and lead to transference-like situations; emotional reactions during childhood (i.e., traumatic events) are reproduced afterwards as "psychological immune reactions" (**Figures 3** and **4**). The underlying mechanism of Post-Traumatic Stress Disorder (PTSD) could also be explained by this process. Interestingly, Klein proposed the "memories in feelings" in her representative book "Envy and Gratitude (Klein, 1957)." The word "memories in feelings" means that strong primitive feelings themselves during childhood are memorized psychologically, and these feelings are reenacted in later life as transference. Klein described such feelings as follows:

> "All this is felt by the infant in much more primitive ways than language can express. When these pre-verbal emotions and phantasies are revived in the transference situation, they appear as 'memories in feelings', as I would call them, and are reconstructed and put into words with the help of the analyst. In the same way, words have to be used when we are reconstructing and describing other phenomena belonging to the early stages of development. In fact we cannot translate the language of the unconscious into consciousness without lending it words from our conscious realm (Klein, 1957)."

This Kleinian mechanism may also be explained by our microglia theory of the psychological immune memory/reaction. Recent epidemiological studies have revealed that maladaptive

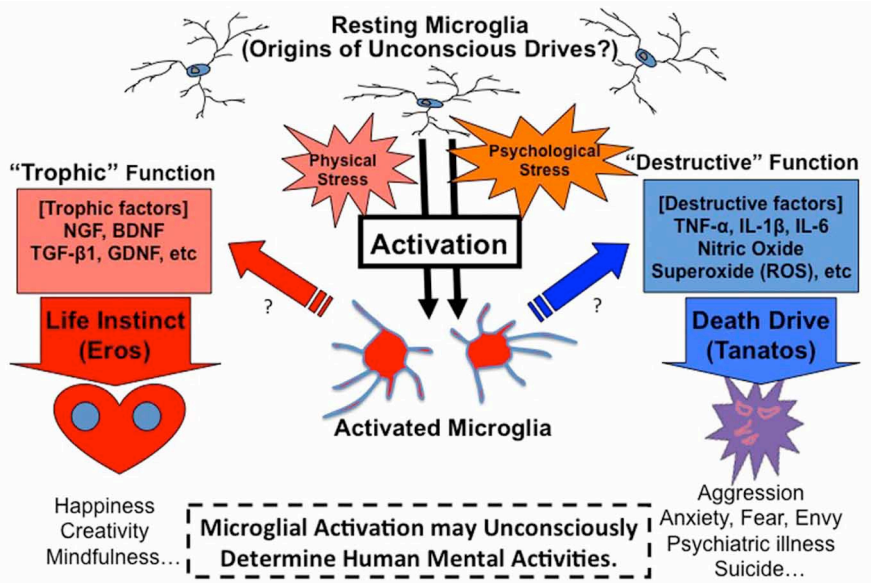


**FIGURE 2 | Microglia theory of unconscious drives.** Microglia may act as the origin of unconscious drives in the mind. Microglia play the role of a double-edged sword in the brain. Microglia release not only maladaptive factors such as TNF-α but also protective factors such as BDNF, which means that microglia are alternately both bad and good actors in the brain. The direction and strength of microglial activation may be the origin of Freud's two essential drives of death (tanatos) and life (eros). "Destructive" function of microglia may play an essential role in *the death drive*. Maladaptive microglial activation caused by a certain psychological/physical stress may induce aggressive, anxious, fearful, and envious states: these states may furthermore lead to psychiatric disorders and suicidal thought/behaviors. On the other hand, "Trophic" function of microglia may play an important role in *the life instinct*. Appropriate stress may activate microglia at good enough levels, which induce protective factors and result in happy, creative and mindful states.

parent-child relationships and childhood trauma are the crucial risk factors for psychiatric disorders in later life (Alvarez et al., 2011; Bebbington et al., 2011; Hovens et al., 2012; Morgan et al., 2012). In addition, a recent report of a human twin study suggests that childhood trauma induces inflammatory reactions (Rooks et al., 2012). Such evidence supports our proposed theory that microglial immune memory may develop psychiatric disorders in later life.

The origin of unconscious processes in the brain especially in psychiatric condition has not been well understood. Our theory may reflect a heightened attempt by microglia to achieve homeostasis in the brain when it is under physical or psychosocial stress. In the process of understanding emotional systems in the brain, neuronal centered explanations have been dominant including the importance of schemata, higher-order conditioning, implicit memory, and experience-dependent shaping of neurotransmitter systems (Solms and Turnbull, 2002; Panksepp, 2004; Welzer and Markowitsch, 2005; Wright and Panksepp, 2012). At present, the connection between the immunological role of microglia and our proposed "psychological immune memory" has not been well clarified. However, a series of studies by Bilbo and her colleagues (Bilbo and Schwarz, 2009; Williamson et al., 2011) and other recent thought-provoking animal studies have suggested interesting physiological outcomes regarding microglial contribution to psychological immune memory and emotional responses. As shown the above, rodent studies have reported that severe stresses including psychosocial stress activate microglia (Frank et al., 2007; Schiavone et al., 2009; Sugama et al., 2009; Tynan et al., 2010; Wohleb et al., 2011; Hinwood et al., 2012a,b). Acute stress is demonstrated to induce morphological microglial activation in several brain regions including the midbrain periaqueductal gray (PAG), an area that plays crucial roles in behavioral and emotional responses to uncontrollable stress, threat, anxiety, and pain. Sugama et al. determined whether neuronal activation may be involved in the stress-induced microglial activation by measuring the correlation between neuronal activity measured as c-Fos expression and morphological microglial activation in the PAG (Sugama et al., 2009). Acute stress was succeeded by morphological activation of microglia and increased c-Fos expression in the PAG, and their analysis demonstrated that microglial activation occurred adjacent to responsive neurons. By contrast, LPS treatment induced microglial activation even in the absence of neuronal responses in the PAG as well as in the rest of the midbrain. Their findings suggest that the mechanism of microglial activation during stress may differ from those of infection or inflammation. Based on their results, Sugama et al. suggested that stress-induced c-Fos protein from activated neuronal cells may play some roles to trigger microglial activation. Recently, Hinwood et al. investigated a series of rodent studies how psychological stress affects microglia (Hinwood et al., 2012a,b). They found that chronic psychological stress increases the internal complexity of microglia, and that chronic stress markedly increases the expression of beta1-integrin (CD29), a protein previously implicated in microglial

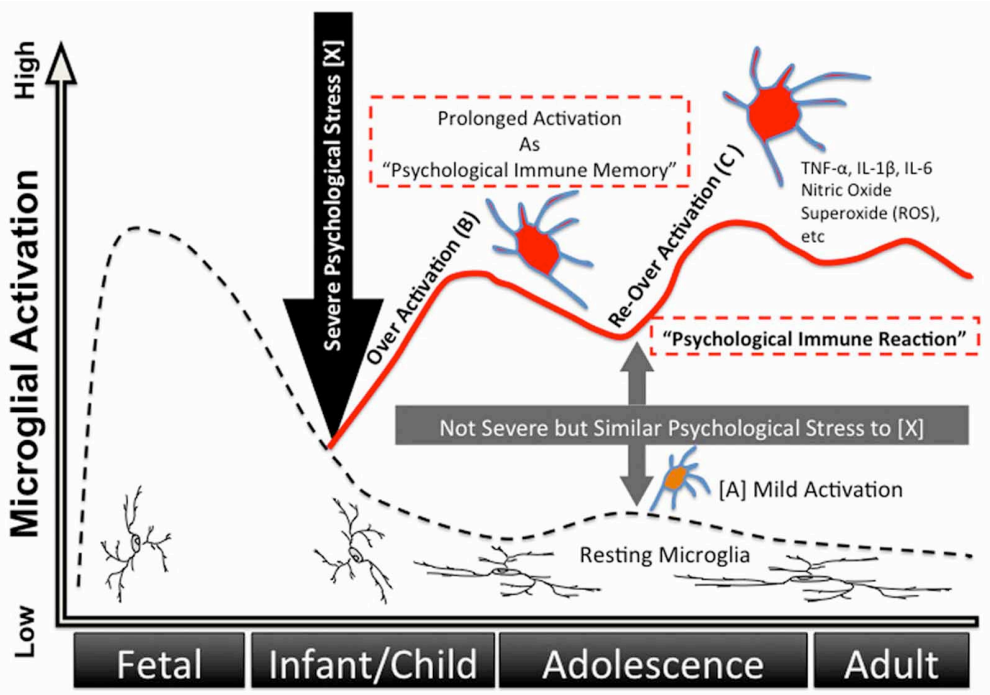


**FIGURE 3 | Developing process of "psychological immune memory/reaction" via microglia.** Microglia have proven to have direct connections with neuronal synapses, and external stress activates microglia via neuronal stimulus. Not only physical stress but also psychological stress activates microglia in animal models. Herein we propose a possible process of microglia activation as "psychological immune memory" during human life. **(A)** Normal daily psychological stress (not extreme stress) moderately and temporarily activates microglia via neuronal stimulus **(A)**. **(B)** Severe psychological stress (e.g., trauma) over-activates microglia via nervous excitement **(B)**, which induces a storm of inflammatory cytokines and free radicals in the brain, thus resulting in abnormal behaviors and strong emotional reactions. In addition, this storm results in damaging neuron-glial networks and the subsequent rebuilding of novel neuro-glial networks. This network change means that previous psychological reactions dramatically change into novel stimulus-output patterns. Moreover, once microglia have been activated strongly, these microglia remain in pre-activated states for years, which we can dub "**psychological immune memory.**" **(C)** Pre-activated microglia **(B)** are excessively responsive to even slight stimuli when the stimuli are similar to the previous traumatic stress, and are again over-activated **(C)**. Similar but slight stress, which was previously only a good enough modulator of microglia, results in a strong storm of the brain/abnormal behavior/strong emotional reaction as that of the previous traumatic reaction. We have dubbed this reaction "**psychological immune response,**" and it can explain many psychological and psychopathological mechanisms such as transference and repeated behavioral/emotional reactions typically seen in PTSD.

ramification (Hinwood et al., 2012b). These findings suggest that beta1-integrin may be one possible modulator between psychological stress, neuronal network activity and microglial ramification (Hinwood et al., 2012b). Above-mentioned animal studies indicate that unconscious drives may involve both activated neurons and/or activated microglia, while it is very difficult to differentiate between clusters of neuronal activation and microglial activation in the process of unconscious brain processes and emotional motivations because of the difficulty of establishing experimental models. Furthermore, to our knowledge, it is also difficult under current scientific conditions to clarify whether microglia are the underlying precipitator of unconscious thought processes and motivations. To our knowledge, the exact process of how microglial and/or neuronal activation affect emotional experience and behavior has not been well understood. Interestingly, a recent animal study has suggested that microglial activation has a positive link to anxiety-like behaviors, and suppressing microglial activation by minocycline results in ameliorating the anxiety-like behaviors (Neigh et al., 2009). This report suggests that microglial activation may, at least to some extent, contribute to the occurrence of anxiety. As introduced the above, microglia are recently known to have continuous direct contact with synapses (Wake et al., 2009). In addition, microglia are known to have various neurotransmitter receptors, and neurotransmitters are reported to affect not only the neuronal system but also microglia (Pocock and Kettenmann, 2007; Kato et al., 2013). Therefore, in our opinion, microglial activation may induce a disturbance of neuron-microglia communication at least to some extent, and neuronal systems, which organize emotional and psychological experience and behavior, may be over-activated. Further studies should be conducted to clarify how microglial activation affects neuronal system, emotional and psychological experience and behavior.

Microglial psychoimmunological memory is a novel concept which we have just recently proposed. To our knowledge, no study has been conducted in this aspect. Traumatic memories may be located within neural networks without having to recur to microglia, or microglia may contribute much to such

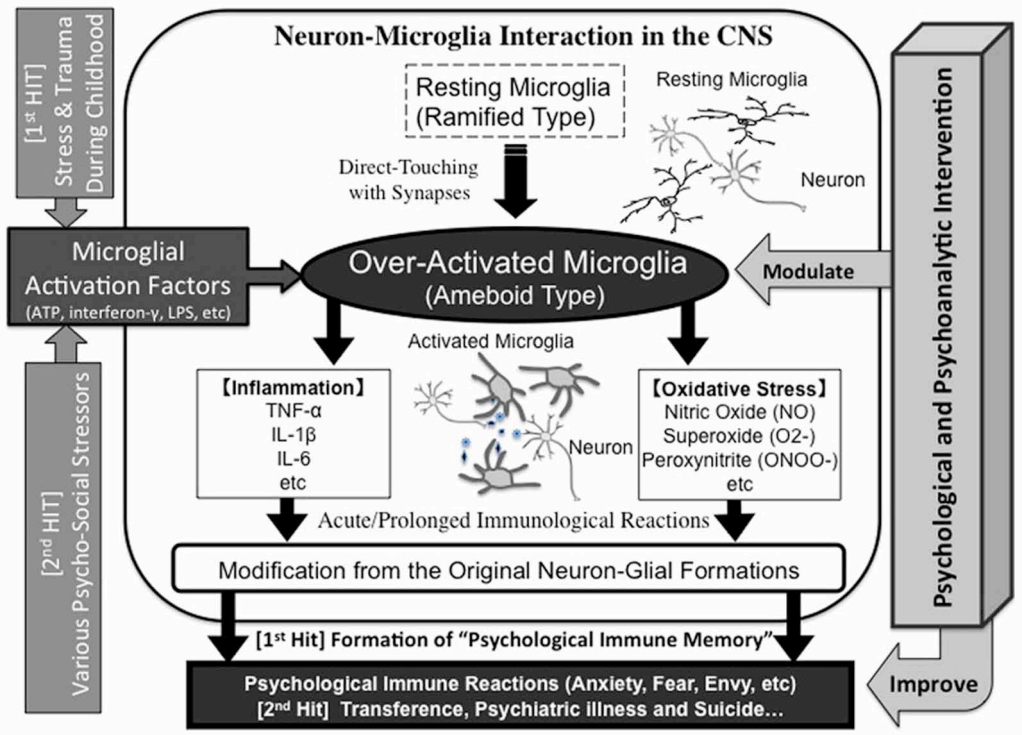


**FIGURE 4 | Neuron-microglia interaction during "psychological immune memory/reaction."** Strong psychosocial stress such as trauma during childhood may over-activate microglia, which induce a variety of inflammatory/oxidative-stress factors and result in damaging the original neuron-microglial formations. Finally, novel neuron-microglial networks will be formulated. This reaction is memorized as "psychological immune memory". When similar psychosocial stress, even at weaker levels, occurs in later life, the primed-microglia may be over-activated. This reaction will also induce various maladaptive psychological reactions, which may result in transference reactions during interpersonal relationships, psychiatric disorders and also suicidal behaviors. On the other hand, psychological and psychoanalytic interventions may improve these states by suppressing microglial maladaptive activation.

memories. Further studies are needed to clarify the relationship between early trauma, emotional behavior and microglial immune reactions.

## SOCIAL INTERACTION AND MICROGLIA IN HEALTHY HUMAN

Until recently no experiment had been conducted focusing on human social and psychological factors in relation to microglia, and there is no known drug with the specific effect of modulating human microglia. Therefore, using minocycline, a tetracycline antibiotic and the most famous microglial inhibitor in rodent models, is one of the best alternative approaches to clarify microglial functions in human social/mental activities. A recent rat study has shown that minocycline suppresses microglial activities not only in stress-induced activation states but also in resting states (Hinwood et al., 2012b). In order to examine how microglia influences social and mental activities, we recently examined how minocycline works in human social decision-making by trust game (Watabe et al., 2012); healthy adult males made a monetary decision about whether or not to trust an anonymous partner after a 4-day oral administration of minocycline. The minocycline group showed a positive correlation between their monetary score in the trust game and their evaluation scores of others' trustworthiness in a questionnaire, but surprisingly the placebo group did not. Thus, minocycline sharpened participants' sense of trust that led them to be more decisive in the game. This first trial has suggested that microglial activation may cause "unconscious noises" against appropriate social decision-making, and inhibiting microglial activity may reduce such noise (Watabe et al., 2012). In a subsequent trial with larger samples, we additionally measured the effects of anxiety and personality (Kato et al., 2012). The monetary score in the trust game was significantly lower in the minocycline group. Interestingly, participants' ways of decision-making were significantly shifted; cooperativeness, one component of personality, proved to be the main modulating factor of decision-making in the placebo group, on the other hand, the minocycline group was mainly modulated by state anxiety and trustworthiness. Our results of the second trial suggest that minocycline led to more situation-oriented decision-making, possibly by suppressing the effects of personality traits, and furthermore that personality and social behaviors might be modulated by microglia. Early life events may activate human microglia, establish a certain neuro-synaptic connection, and this formation may determine personality and personality-oriented social behaviors in later life (Kato et al., 2012).

The above-mentioned findings shed new light on the dark side of microglial social/mental functions in humans, especially highlighting the role of microglia for the unconscious. In the same way that Freud proposed that our behaviors must be controlled by the unconscious world, microglia may unconsciously control our behaviors. Human neuroscience focusing not only on computer-like neuronal networks but also on "noisy" microglia would be a novel key for investigating "noisy" human social/mental activities that are unlike "noiseless" computers. To explore these mechanisms, further translational research is needed.

## MICROGLIAL DOUBLE-EDGED SWORD AND AMBIVALENCE

Microglia play an interesting role as a double-edged sword in the brain (Henkel et al., 2009; Graeber and Streit, 2010). Microglia release not only maladaptive factors such as Tumor Necrosis Factor (TNF)-α but also protective factors such as Brain-Derived Neurotrophic Factor (BDNF), which means that microglia are alternately both bad and good actors in the brain. "Destructive" function of microglia may play a vital role in *the death drive*. On the other hand, "trophic" function of microglia may play an equally essential role in *the life instinct*. It remains controversial as to whether the origin of the two drives is the same from the psychoanalytic perspective. Based on our microglial theory, the origin and the determinant factor may be the composition and the direction of the microglia. Microglia are known to express different *faces* during developmental, adolescent and adult stages. The balance-shift of the trophic/destructive expression of microglia may explain the underlying origin of the two drives in the mind. The existence of two directional microglia in the same region may induce an ambivalence, which means a dilemma between the two directional emotions such as "love and hate." The direction of microglial activation may determine our behaviors toward life or death (**Figure 2**).

Our terms "trophic" and "destructive" microglia should not be taken in a strictly literal sense. Our proposed theory may be too oversimplified in implying that the function of microglia easily divides into (A) "trophic" function of microglia = preserving = the life instinct, and (B) "destructive" function of microglia = destroying = the death instinct. This dichotomy is not always true in real situations. Some microglia might destroy for synaptic pruning, which in the long run is a trophic result for the brain, to preserve energy for more frequently functioning neuron populations, and to reconstruct more appropriate neuronal networks. Furthermore, we could apply this proposed neuroscientific process into human psychological development as follows: It is somewhat essential to have painful/stressful experiences in developing periods, during which microglia may activated, and neuronal networks may be reformed, and finally rebuilt a more prosocial personality and/or resilient self in later life. However, for some, this process might not work through, and result in pathological/psychiatric conditions. It is not known how differentiate destructive processes that are useful, from destructive processes that are associated with pathology, while we prospect that these different outcomes might be determined by factors such as genetic vulnerability, extremely painful/stressful events, dysfunction of neurons/microglia, and environmental factors before/after these events. For example, some volume of microglia-releasing mediators such as pro-inflammatory cytokines and/or free radicals may be essential for our mental development; however microglia in some individuals may easily release too much of such mediators even after weak stressful events. Those individuals may easily be prone to psychiatric conditions. At least to some extent, recent neuropsychoanalytic theories such as the Panksepp's SEEKING system (Wright and Panksepp, 2012) and Kernberg's "death drive" theory (Kernberg, 2012) may be complemented by our proposed microglial theory. Digging up these interactions provide for further translational research opportunities to bridge the huge gap between the brain and the mind. Aging is known to be one of the key switching factors of microglial characteristics. Generally speaking, aging tends to activate microglia maladaptively (Dilger and Johnson, 2008; Jang and Johnson, 2010; Norden and Godbout, 2012), which may provide a clue to clarify these underlying mechanisms.

## POSSIBLE MICROGLIAL CONTRIBUTION TO THE CONSCIOUS AND THE UNCONSCIOUS WORLD

It is of great importance to understand the present situation of affective neuroscience and neuropsychoanalysis including the biological understanding of the unconscious/conscious. To our knowledge, all previous research has been focused solely on neuronal systems including synapses to understand the emotional reactions and the unconscious in the brain. It is a novel challenge to consider the role of microglia in emotional reactions and the unconscious. Neuronal systems and neurotransmitters have been regarded to have important roles in "unconsciously" modulating emotions and motivational behaviors (Solms and Turnbull, 2002). In addition, microglia may be one possible source of "unconsciously" generated negative emotions that do not directly rely on perceptual input but are generated biologically. Herein we hypothesize a possible role for microglia in emotional reactions. The following three processes might be occurring at least in some biological pathways of the unconscious/conscious; (Process I) microglia may be activated by neurotransmitter modulations connected with emotional reactions based on perceptual inputs, (Process II) microglial activation may modulate synaptic reactions via neurotransmitters resulting in emotional reactions, and (Process III) a mixed process of I and II may occur especially during continuous high emotional responses, in which primary emotional reactions may activate neuronal systems via synapses and neurotransmitter modulations, resulting in microglial activation, and finally mutual activation may occur via neurotransmitters and microglial mediators such as free radicals and/or cytokines. We hypothesize that process III may be one of the possible causes for emotional disturbance, symptoms of various psychiatric disorders and also suicide.

In addition, we now present a possible mechanism of the conscious and the unconscious in the brain. The system of the relationship between the conscious and the unconscious has long been considered within the context of neuronal systems. Microglia are now known to be very unique dynamic cells in the brain, which can move around and are usually independent from neuronal systems, and sometimes have direct contact with

synapses. These roles seem to be similar to Freud's perceptual theory called "the system Pcpt.-Cs., or the system W-Bw, which was named after the German words Wahrnehmung (= perception; Pcpt.) and Bewußtsein (= consciousness; Cs.)" (Freud, 1920). We suppose that microglial activation itself does not directly equate to emotional reactions, but we suggest that microglial activation may be one of the crucial priming factors of the unconscious for emotional reactions by affecting neuronal systems. It is easily understood that external inputs trigger emotional reactions, while the mechanism of emotional reactions without external input such as nightmares has not been fully comprehended. Our theory may shed new light on the understanding of internally caused (or the unconscious-derived) emotional reactions. Interestingly, microglial contribution has recently been suggested in the occurrence of delirium, which induces disturbance of the conscious by internal causes such as systemic infections (Van Gool et al., 2010). Our theory might give us the chance to re-translate Freudian theory of the system between the conscious and the unconscious. Further studies should be highlighted in this aspect.

## CONCLUSION

### FUTURE PERSPECTIVES

In this paper, we showed the possibility that microglial activation in the brain activates unconscious drives in the mind. We also presented the brain/mind structural system of ambivalence, transference, psychological trauma and even the Oedipus complex by importing the microglia theory of "psychological immune memory/reaction." In addition, we introduced a recent human study focusing on the microglial role of social decision-making. Finally, we showed a possibility that direction and context of microglial activation may be a key factors in our mental activities including unconscious world.

Previously, Eric Kandel explored the neuron-synaptic world based on his psychoanalytic background as a novel work of the 20th century (Kandel, 1979, 1999, 2005). In a similar mode to Kandel's exploration, the novel scientific field, now highlighted as "neuropsychoanalysis" (Fonagy, 2001; Solms and Lechevalier, 2002; Solms and Turnbull, 2002; Panksepp, 2007; Northoff, 2011; Panksepp and Solms, 2012), has endeavored to clarify the underlying mechanism of the unconscious and psychoanalytic theories from a neuroscientific perspective. In the 21st century, new challenges focusing on microglia should be explored in the new world of the mind/brain beyond Kandel's neuron-synaptic doctrine. We believe that our proposed theory sheds new light on solving deeper mechanisms of "unconscious drives" from both psychoanalytic and neuroscientific perspectives. Microglia may have the potential to bridge the huge gap between neuroscience, biological psychiatry, psychology, and psychoanalysis. Further communication between neuroscientists, psychiatry, psychologists, and psychoanalysts is required. To investigate the microglia theory, further translational research from *in vitro*/*in vivo* animal studies to human studies is needed based on the neuropsychoanalytic approach. Finally, we highlight some research questions of particular importance to be clarified:

- What is the key interaction between microglial activation (biological world) and the unconscious (psychological world)?
- What kind of afferent networks (afferent stimulus, input, impulse, etc.) and molecules such as neurotransmitters activate microglia under psychosocial stress?
- How do activated microglia act on efferent neuronal pathways, and how do microglia finally impact on the unconscious, emotions and behaviors? In relation to cognition, various studies suggest the positive link between microglial activation and dementia which is one of the most typical phenotypes of cognitive dysfunction, while the underlying mechanism between dementia's cognitive dysfunctions and microglial activation are less well understood. Can microglia modulate various cognitive functions under not only pathological states but also normal states? It is also unclear how microglia activation influences neurotransmitters and/or neural systems involved in emotional and experience and behavior and how microglial activation back-project to the mental and behavioral realm, while the following evidence may give a cue for future investigations. Not only neurons but also microglia have a variety of neurotransmitter receptors including dopamine and noradrenaline receptors (Pocock and Kettenmann, 2007; Kato et al., 2013), which are closely related to our mental activities and the pathophysiology of neuropsychiatric disorders. Sugama et al. showed that acute stress activates microglia in the PAG (Sugama et al., 2009). In addition, Neigh et al. suggested that microglial activation induce anxiety-like behaviors in mice (Neigh et al., 2009). These reports suggest that microglial activation may contribute to various emotional reactions.
- Microglia are thought to be a heterogeneous group. Therefore, we should investigate the actions of microglia in each group. Regional specificity might exist, and it may link to previously known understandings in psychiatric brain imaging studies.
- Microglial modification may create a novel strategy for intervention in psychiatric disorders. Clinical trials focusing on microglia should be conducted.
- Microglia have mutual communications not only between neurons but also astrocytes and oligodendrocytes. Therefore, mutual interaction of neuron-glia should be clarified to understand the deeper mechanisms of unconscious and neuropsychoanalytic theory in the brain.

## FINAL REMARKS

Before developing psychoanalysis in the late 19th century, Freud sketched the neuronal mechanism of the mind (**Figure 1**), and Freud might have possibly dreamed that biological explanations of the unconscious mind would one day replace psychological ones (Freud, 1950 [1895]). Microglia may be a key player to realize Freud's long-unresolved dream.

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# Harnessing psychoanalytical methods for a phenomenological neuroscience

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Psychoanalysis proffers a wealth of phenomenological tools to advance the study of consciousness. Techniques for elucidating the structures of subjective life are sorely lacking in the cognitive sciences; as such, experiential reporting techniques must rise to meet both complex theories of brain function and increasingly sophisticated neuroimaging technologies. Analysis may offer valuable methods for bridging the gap between first-person and third-person accounts of the mind. Using both systematic observational approaches alongside unstructured narrative interactions, psychoanalysts help patients articulate their experience and bring unconscious mental contents into awareness. Similar to seasoned meditators or phenomenologists, individuals who have undergone analysis are experts in discerning and describing their subjective experience, thus making them ideal candidates for neurophenomenology. Moreover, analytic techniques may provide a means of guiding untrained experimental participants to greater awareness of their mental continuum, as well as gathering subjective reports about fundamental yet elusive aspects of experience including selfhood, temporality, and inter-subjectivity. Mining psychoanalysis for its methodological innovations provides a fresh turn for the neuropsychoanalysis movement and cognitive science as a whole – showcasing the integrity of analysis alongside the irreducibility of human experience.

**Keywords: phenomenology of consciousness, phenomenology, first-person perspective, subjective experience, neuroscience methods**

## INTRODUCTION

This paper illustrates how the marriage of phenomenology and psychoanalysis can inform the scientific study of consciousness. In particular, we outline the potential psychoanalysis holds as a tool for fostering different states of awareness and gathering experiential accounts for the purposes of cognitive neuroscience. Methods for elucidating the structures of phenomenal experience are scantily present in the landscape composing the cognitive sciences. This lacuna – a palpable gap between subjective and objective techniques – calls for expert methods to discern and describe experience from first and second person perspectives. While readily embracing psychodynamic theory, proponents of the neuropsychoanalysis movement have largely overlooked the methods inherent to analysis. A central aspect of the psychoanalytic approach, the unstructured narrative interaction forms the backbone of analysis. Though unconventional in the context of experimental neuropsychology, to disparage the narrative dynamic would cripple the research potential of psychoanalysis (Bazan, 2011). For example, cognitive scientists stand to benefit from narrative approaches to guide participants to uncover unconscious aspects of their experience, cultivate meta-awareness, and elicit descriptive firsthand reports. Here we argue that viewing psychoanalysis as a method for elucidating subjective experience best motivates collaboration between neuroscience and psychoanalysis. Sketching the crux of contemporary neuropsychoanalysis, we highlight the relative merits of a crosstalk with the critical neuroscience movement of neurophenomenology. We conclude by discussing how the development of new phenomenological techniques may leverage psychoanalytic methods in the clinical and experimental study of consciousness.

## NEUROPSYCHOANALYSIS IN FLUX

Neuroscientists, as well as psychoanalysts, are still trying to determine the nature of their collaboration in the burgeoning field of neuropsychoanalysis. Controversy regarding the relationship between psychoanalysis and the natural sciences dates back to Freud's time, and continues to garner much attention today (Cohler and Galatzer-Levy, 2007). While some scholars consider neurobiology and psychoanalysis to be epistemologically and terminologically irreconcilable (Borch-Jacobsen and Shamdasani, 2011), the organic basis of mental life is one of the founding tenets of psychoanalysis (e.g., Freud, 1910b, p. 209). Freud (1895) had anticipated a future in which the psychological and neural sciences would coalesce. Since the 1990s, this vision has gradually come to fruition: while neuroscientists and cognitive psychologists have rekindled their interest in psychoanalytic ideas, analysts have increasingly turned toward the biological sciences (Fotopoulou et al., 2012). Overarching arguments continue to suggest that neuropsychoanalysis binds neuroscience and analysis by facilitating a crosstalk on topics of mutual interest (Solms and Turnbull, 2011). These global accounts inspire leading contemporary scholars to follow this intuitive lead and expound on the details of this cooperation.

Most research under the label of "neuropsychoanalysis" seeks to situate the concepts of psychoanalysis within the framework of contemporary neuroscience. Early collaboration, in the spirit of Freud, centered on understanding neuropathology from a psychodynamic perspective (Kaplan-Solms and Solms, 2000). This manner of clinically oriented investigation has since expanded to include studies of pathological behavior (e.g., depression and anxiety, Zellner et al., 2011), the neural mechanisms of psychodynamic psychotherapy (Gerber, 2011), as well as attempts to find biological measures for therapeutic outcomes (Shedler, 2010). Other research in neuropsychoanalysis fits with the preclinical cognitive neuroscience of consciousness. These investigations aim to develop models of the brain that accommodate and illuminate psychoanalytic phenomena such as repression (Bazan and Snodgrass, 2012), libido (Pfaff and Fisher, 2012), the dynamic unconscious (Shevrin et al., 1996; Berlin, 2011; Solms and Zellner, 2012), and dreaming (Zellner, 2013). As the investigatory domain of contemporary neuropsychoanalysis grows, so does the variety of empirical approaches: from neuroimaging techniques to experimental behavioral methods and animal studies (Fotopoulou et al., 2012).

Some analysts view neuropsychoanalysis as a weight on psychoanalytic discourse. Such clinicians see the movement as perpetuating the view that psychoanalysis needs biological bolstering to be complete, legitimate, and relevant (Blass and Carmeli, 2007). Other scholars have been especially critical of neuropsychoanalysis, suggesting that it could taint quality, and understanding of analysis among clinicians (Hoffman, 2009). These claims likely emerge in response to studies that purport to investigate the "scientific validity" of psychoanalytic theories (cf dream theory in Shirley, 2011). Alas, such scientism runs counter to the very epistemology set forth by the founders of neuropsychoanalysis, who encourage a balance between scientific objectivity and the subjective insights of psychoanalysis (Fotopoulou et al., 2012). Other critics argue that neuroscience is irrelevant to clinical practice, as the latter emphasizes uniquely personal accounts that are scantily amenable to scientific generalization (Pulver, 2003; Mechelli, 2010). Proponents of neuropsychoanalysis typically respond that while the entire spectrum of neuroscientific studies may be less clinically relevant to psychoanalysts, some studies undoubtedly are, for example animal studies that shed light on primal emotional behavior (Panksepp and Solms, 2012). And while concerns about the integrity of clinical practice remain an important issue, analysts also warn against an insular psychoanalysis that fails to engage in a constructive and critical dialog with the larger scientific community (Safran, 2012).

The collaboration between neuroscience and psychoanalysis reflects greater questions about the nature of scientific research, discourse, and validation (Aron, 2012). By incorporating phenomenological domains into traditional experimental paradigms, neuropsychoanalysis are reshaping the boundaries of science. Findings from neuroscience, moreover, increasingly govern our popular conceptions concerning behavior, psychopathology, and what it means to be human (Thornton, 2011; Young, 2011). Neuropsychoanalysis, therefore, joins the critical neuroscience movement in engaging the scientific community with discussions about culture, meaning, and the irreducibility of human experience (Choudhury and Slaby, 2011). Within this overarching search to unravel the relationship between the mind and body, a central question looms: can the objective third-person methods of cognitive science account for the first-person experience of subjective mental life?

## NEUROPHENOMENOLOGY AND THE PROBLEM OF CONSCIOUSNESS

The question of how and why humans are conscious – known amongst philosophers as the "hard problem" of consciousness – has provoked major debate concerning the nature of scientific inquiry. Most scientists posit that biological mechanisms subserve conscious experience, albeit little knowledge informs the details of such mechanisms (Chalmers, 1995, 2002). Neurologists have long recognized that we seem able to account for the workings of the human brain without recourse to influences beyond the laws of physical science (Eccles, 1965). Subsequently, many thinkers feel hard-pressed to speculate on the evolutionary and functional role of consciousness (Harnad, 2002). Such questions have led some philosophers to the conclusion that consciousness is an illusory heuristic (Churchland, 1981). These thinkers argue that conscious experience *just is* the neurobiological correlate of consciousness – a position that most neuroscientists hold as their "spontaneous philosophy" (Varela, 1998, p. 31; Dennett, 2001). Others disagree and argue that a description of mind that refers only to biological substrates and processes necessarily leaves something out. These scholars insist that consciousness is irreducible to information processing in the brain (Velmans, 2009) and emphasize that our conscious experience presupposes "every statement, model, or theory" of natural science (Thompson, 2004, p. 394). Such philosophical discord persists, reflecting and motivating practical challenges in the study of consciousness at the experimental level.

One response to the puzzle of consciousness comes from *neurophenomenology*, a movement founded by Varela et al. (1992). According to Varela, the hard problem is established on a deeply ingrained, falsely dualistic understanding of mind and brain. Instead of trying to philosophically "solve" the hard problem, he proposed that cognitive scientists take a methodological approach (Varela, 1996). In order to elucidate how and why experiences arise from neural processes, scientists require careful descriptions of experience to match the refined objective descriptions of brain functioning (Jack and Shallice, 2001; Lutz, 2002); however, researchers have largely eschewed such first-person methods. This trend partly owes to the recent focus in cognitive science on imaging of the living human brain alongside a long-standing ambivalence towards introspective reports (Nisbett and Wilson, 1977). Thus, while researchers are now equipped with many advanced methods for imaging and modeling the brain in fine-grained detail, sophisticated methods for describing and discriminating subjective experience continue to lag behind. Varela advocated bridging this methodological gap by incorporating the experiential techniques of phenomenology into a circulating dialog with the third-person methods of cognitive science. His neurophenomenology seeks to give an "explicit and central role

to first-person accounts and to the irreducible nature of experience, while at the same time refusing both a dualistic concession or a pessimistic surrender" (Varela, 1998, p. 32). In doing so, neurophenomenology does not solve, but rather "dis-solves" the hard problem (Varela, 1998).

Proponents of Varela have realized the neurophenomenological project in different forms and under a variety of labels. Some scholars focus on the philosophical details of the collaboration between phenomenology and cognitive science (Gallagher, 2003). These theorists tease apart difficult phenomenological issues, such as the nature of indexing the self (Zahavi and Roepstorff, 2011), and conducting investigations into experiential realms pertinent to clinicians, including the phenomenology of psychopathology, (e.g., Sass et al., 2011). Neurophenomenology is also a growing scientific research program that seeks to modify and complement traditional methods of neuroscience for better phenomenological inquiry. For example, cognitive scientists have adapted a neuroimaging paradigm to allow for periodic "experience sampling" of subjects during experiments (Christoff et al., 2009). Some investigators utilize experimental participants who are already expert at observing and describing their experience, such as Buddhist meditators (Farb et al., 2007; Lutz et al., 2008). Other scholars have proposed that researchers may harness hypnotic and posthypnotic suggestion to alter subjective experience and encourage particular states of awareness (Lifshitz et al., 2013, 2014). One group of researchers in neurophenomenology focuses on developing first-person methods (Depraz et al., 2003; Vermersch, 2009) as well as second-person interviewing techniques for aiding subjects in attending to and articulating their experience (e.g., Petitmengin, 2006). Across all approaches, both theoretical and applied neurophenomenologists aim to bind first-person approaches with the techniques of modern cognitive science to uncover the basic structures of consciousness (Gallagher and Schmicking, 2010).

Psychoanalysis seems apposite to the goals of neurophenomenology; yet neurophenomenologists have largely overlooked psychoanalytic techniques and theories. Instead, neurophenomenologists have turned to two main sources of inspiration: Western Phenomenology (e.g., following philosophers such as Heidegger, Husserl, and Merleau-Ponty; see Schmicking, 2010) and Eastern contemplative traditions including Buddhist practices (Thompson, 2006; Schmicking, 2010). Research in neurophenomenology centers on training or guiding participants to discern and describe their experience with awareness and impartiality (Petitmengin and Bitbol, 2011). The neurophenomenology approach encourages individuals to reflexively observe consciousness from their first-person perspective and to recount accurate and detailed subjective reports (Lutz and Thompson, 2003). Although the inclusion of psychoanalysis in the neurophenomenological toolbox has yet to occur, Western Phenomenology, and psychoanalytic theory do overlap (Karlsson, 2010; Csordas, 2012). Indeed, the existential psychiatry movement of the early 20th century bridged the two disciplines in letter as well as in spirit (Halling and Dearborn Nill, 1995). Moreover, current efforts in neurophenomenology such as the "explicitation interview" harken to psychoanalytic techniques. The explicitation interview is a practice of "guided retrospective introspection" that incorporates inter-subjective guidance and non-leading suggestions to promote awareness of processes that typically remain implicit and un-seen within the field of experience, also known as "meta-awareness" (Maurel, 2009; Vermersch, 2009). Similarly, analysts describe the therapeutic process as "making the unconscious conscious" and commonly gage the completion of analysis by when the patient can freely articulate whatever comes to mind (Freud, 1910a; Wachtel, 2012). Thus, psychodynamic methods already suffuse established neurophenomenological protocols for cultivating meta-awareness in untrained participants.

The motives and objectives of neurophenomenology resonate with the call to neuropsychoanalysis. Both movements point to the need for a psychological theory in neuroscience that avoids fracturing or reducing human experience into a collection of functions and abilities. Just as neurophenomenologists emphasize the "embodied mind" (Clark, 1999; Thompson and Varela, 2001), neuropsychoanalysts urge scholars to reimagine the "minded brain" (Panksepp and Solms, 2012). Both groups argue that without a theoretical framework that operates at the level of the subject, neuropsychology fails to capture the psychological at all (Bazan, 2011), as well as stress the need for a "neurophenomenal level of analysis" in experimental neuropsychology (Panksepp and Solms, 2012). Like its phenomenological counterpart, neuropsychoanalysis can be seen as a direct effort against the implicit biological reductionism in cognitive neuroscience. Current research in the neuropsychoanalysis community appears biased toward the traditional methods of cognitive neuroscience. To analysts, collaboration with cognitive neuroscience runs the risk of reducing psychoanalytic "meaning" to neural "cause." In line with the outlook Varela espoused, a turn toward the methodological in neuropsychoanalysis could help assuage these concerns, shifting the emphasis from psychoanalytic theory (e.g., testing the scientific validity of psychoanalytic concepts) to psychoanalytic methods (e.g., incorporating technical aspects of the therapeutic process into experimental protocols). However, while both neurophenomenology and neuropsychoanalysis call for a theory of experience at the subject level, only the former has generated an empirical program for incorporating that theory in practice. In closing, therefore, we propose that neuropsychoanalysis may present a new incarnation of neurophenomenology.

## CONCLUDING REMARKS

The practical realization of neuropsychoanalysis-as-neurophenomenology presents many challenges. For example, is it possible to harness elements of the intuitive therapeutic process in an experimental context? Whereas Varela called upon Western phenomenology and Eastern contemplative traditions for their systematic treatment of firsthand experience, analysts often cite one of the hallmarks of psychoanalysis as the "imprecise" treatment of firsthand experience (Bazan, 2011, p. 2). Written accounts of therapeutic methods (e.g., the specific strategies that an analyst employs to bring out the unconscious stories of their patients) tend to take the form of case studies. Descriptions of more universal or underlying therapeutic techniques are sparse; analysts train *in vivo*, by engaging in clinical internships and undergoing analysis themselves. While philosophers and analysts have

considered the mechanism of psychoanalytic insight and the relation between psychoanalytic insight and the structures of experience as described by cognitive and phenomenological science, these topics remain largely pristine on the proverbial "To Do" list of neuropsychoanalysis research (Strachey, 1934; Karlsson, 2010). And yet, phenomenology and psychoanalysis both draw on the premise that the vague nature of experience hardly precludes its careful articulation, analysis, and interpretation. A dialog between neuropsychoanalysis and neurophenomenology, therefore, would engender more precise ideas concerning the specific psychoanalytic techniques that can inform a correlation between firsthand descriptions of experience and third-person data.

One approach would advocate for including individuals who have undergone analysis as neurophenomenology participants. In the same way we treat seasoned meditators or phenomenologists, we can exploit the process of discerning and describing the psychoanalytic experience. This idea is scarcely new among analysts: "(One) might manipulate different neuropeptides, in research participants who are themselves psychoanalysts, and then have them describe their subjective states, using their expertise in doing so (with reference to the theoretical concepts that we use). Approaches such as this are rather radical, but they have huge potential, and appear to be remarkably underappreciated" (Solms and Turnbull, 2011, p. 9). To consider analysts and analysands experiential experts on par with, say, trained meditators raises many a problem. And yet, experiments involving either psychoanalytically trained individuals or Buddhist monks would both necessarily involve a second-person component – such as the explicitation interview – thereby exploiting a similar experimental approach.

Spanning an array of literature from clinical science and consciousness research, here we show how neurophenomenology casts a fresh light on the neuropsychoanalysis movement. While proponents of neuropsychoanalysis emphasize the importance of bringing a subject-oriented approach to cognitive neuroscience, these scholars have largely neglected the task of incorporating psychodynamic methods in an experimental setting. Cognitive scientists, however, stand to benefit from drawing on psychoanalytic techniques. Given their expertise in calling the unconscious mind to awareness, analysts could help researchers promote meta-awareness and gather subjective reports that effectively describe the structures of experience. At the same time, focusing on the possibilities of methodological exchange between neuroscience and psychoanalysis offers an answer to concerns within the neuropsychoanalysis community. Rather than foisting neuroscientific methods and models onto the theories of psychoanalysis, mining analysis for its phenomenological capabilities would ensure the integrity of the psychodynamic identity in a domain increasingly tinged with neuro-reductionism. Such an approach would allow neuropsychoanalysis to flourish because of, rather than despite, the different perspectives of its comprising disciplines.

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