Journal of Clinical and Experimental Neuropsychology

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ncen20

SEEKING and depression in stroke patients: An exploratory study

Marina Farinelli [a], Jaak Panksepp [b], Laura Gestieri [a], Maria Rosaria Leo [c], Raffaele Agati [d], Monica Maffei [d], Marco Leonardi [d e] & Georg Northoff [f]

[a] Clinical Psychology Service, "Villa Bellombra" Rehabilitation Hospital, Bologna, Italy

[b] Center for the Study of Animal Well-Being, Department of Comparative Anatomy, Physiology and Pharmacology, College of Veterinary Medicine, Washington State University, Pullman, WA, USA

[c] Physiatric Service, "Villa Bellombra" Rehabilitation Hospital, Bologna, Italy

[d] Neuroradiology Unit, "Bellaria" Hospital, IRCCS Institute of Neurologic Sciences, Bologna, Italy

[e] Department of Specialistic, Diagnostic and Experimental Medicine, University of Bologna, Bologna, Italy

[f] Mind, Brain Imaging and Neuroethics, Institute of Mental Health Research, University of Ottawa, Ottawa, ON, Canada

Version of record first published: 04 Mar 2013.

To cite this article: Marina Farinelli , Jaak Panksepp , Laura Gestieri , Maria Rosaria Leo , Raffaele Agati , Monica Maffei , Marco Leonardi & Georg Northoff (2013): SEEKING and depression in stroke patients: An exploratory study, Journal of Clinical and Experimental Neuropsychology, DOI:10.1080/13803395.2013.776009

To link to this article: http://dx.doi.org/10.1080/13803395.2013.776009

Journal of Clinical and Experimental Neuropsychology, 2013
http://dx.doi.org/10.1080/13803395.2013.776009

SEEKING and depression in stroke patients: An exploratory study

Marina Farinelli[1], Jaak Panksepp[2], Laura Gestieri[1], Maria Rosaria Leo[3], Raffaele Agati[4], Monica Maffei[4], Marco Leonardi[4,5], and Georg Northoff[6]

[1]Clinical Psychology Service, "Villa Bellombra" Rehabilitation Hospital, Bologna, Italy
[2]Center for the Study of Animal Well-Being, Department of Comparative Anatomy, Physiology and Pharmacology, College of Veterinary Medicine, Washington State University, Pullman, WA, USA
[3]Physiatric Service, "Villa Bellombra" Rehabilitation Hospital, Bologna, Italy
[4]Neuroradiology Unit, "Bellaria" Hospital, IRCCS Institute of Neurologic Sciences, Bologna, Italy
[5]Department of Specialistic, Diagnostic and Experimental Medicine, University of Bologna, Bologna, Italy
[6]Mind, Brain Imaging and Neuroethics, Institute of Mental Health Research, University of Ottawa, Ottawa, ON, Canada

The concept of SEEKING describes a predisposition to search enthusiastically for rewards in the environment. While SEEKING and its underlying functional anatomy have been extensively investigated in animals, such processes in humans, especially brain-damaged individuals, remain understudied. We therefore conducted an exploratory behavioral study in stroke patients to investigate the effects of brain lesions that anatomically could be interpreted to impact the SEEKING system and predicted relationships to depression. Patients with lesions in anterior, medial, and/or subcortical lesions showed significantly lower SEEKING scores and higher depression scores than nonlesioned subjects in the control group. Based on our data and related work on animals, we propose central involvement of the anterior subcortical–cortical midline system as core of the limbic system in SEEKING in humans.

Keywords: SEEKING; Depression; Stroke; Affective neuroscience; Rehabilitation.

INTRODUCTION

Panksepp (1998) first proposed an "affective neuroscience" approach to explore foundations of human and animal emotions in connection with specific brain systems. In particular, four basic emotional systems (SEEKING, ANGER, FEAR, and LUST) were identified that have evolutionally deep reptilian roots and three (CARING, SADNESS, and PLAY) that reflect more uniquely mammalian adaptations (Panksepp & Biven, 2012). The Affective Neuroscience Personality Scales (ANPS) have been developed to evaluate these emotional, personality tendencies in humans (Davis & Panksepp, 2011; Davis, Panksepp, & Normansell, 2003). Please note, the full capitalization nomenclature is a scientific terminology to highlight that a specific primary-process emotional system is being discussed (Panksepp, 2011a). The above systems are subcortical networks, and, in general, lower subcortical brain regions have evolutionary primacy in generating basic emotions. The basic

We would like to thank all the patients who took part in this study and to the three anonymous referees whose suggestions and helpful comments allowed us to improve the paper. We are grateful to D. Albarello for statistical computations, N. Marasti, P. Buttazzo, and the "Villa Bellombra" Rehabilitation Hospital (Bologna, Italy) for supporting our research and the Clinical Psychology Service. Many thanks to A. Bordini, E. Lucchi, and M. Turriciano for their contribution to data collection and organization. The study was financially supported by grants from the Canadian Institutes of Health Research (CIHR) and Hope for Depression Research Foundation to Georg Northoff and Jaak Panksepp.

Address correspondence to Marina Farinelli, Via Bellombra, 24, 40136 Bologna, Italy (E-mail: marina.farinelli@unibo.it).

emotional systems cited above not only generate instinctual behavioral responses, but are closely linked to subjectively experienced primal affects that accompany those types of emotional arousal (Panksepp, 2011b, 2011c). In contrast, learning and higher brain functions are critically dependent on higher, more recently evolved brain functions that are conceptualized as secondary and tertiary processes (Northoff, Pengmin, & Feinberg, 2010; Panksepp, 2011b).

As originally proposed by Panksepp (1981, 1982), and conceptually and empirically developed to the present day (Alcaro & Panksepp, 2011; Wright & Panksepp, 2012), the SEEKING disposition is characterized by instinctual behavioral tendencies that help organisms to attend, move, explore, and approach goal-objects—via many actions such as invigorated exploratory locomotion, orientation, specific types of head and body movements, eye saccades, sniffing in olfactory creatures, and sensorial investigation of many nonaversive objects that are confronted during foraging. This system, which contributes to the expression of many other emotions (e.g., LUST, CARE, and PLAY), has traditionally been called "The Brain Reward System" (Coenen, Schlaepfer, Maedler & Panksepp, 2011; Olds & Milner, 1954), presumably generating "pleasurable" sensations—which is not empirically well supported—with little consideration of the appetitive/desire types of feelings that it actually generates.

Many lines of evidence indicate that "SEEKING" is rooted in highly characteristic psychobehavioral and neurobiological processes that drive organisms to pursue and interact with a great variety of specific environmental goal objects; it is a system that is typically active before the organism has formed detailed cognitive or perceptual representations of those objects, and when it has been molded by learning, it is active in anticipation of rewards, rather than during the pleasure accompanying consumption of rewards. Due to its intrinsic positive affective value, the activation of SEEKING is experienced by organisms as a positive affectively desirable state, and hence "rewarding" per se, without the need for any traditional forms of consummatory activity and explicit sensory rewards. In other words, animals vigorously self-stimulate this system when allowed to control brain stimulation along the trajectory of the major underlying pathway, the medial forebrain bundle (MFB). Therefore, the SEEKING view grants organisms a mental life, specifically affective emotional states created from complex, large-scale unconditioned neural dynamics that constitute the psychobehavioral foundation for organismic existence (Alcaro, Huber, & Panksepp, 2007; Alcaro & Panksepp, 2011). The SEEKING system not only promotes exploration, investigation, and foraging but also permits many other emotional urges to become energized with forms of appetitive and anticipatory arousal (Davis & Panksepp, 2011; Wright & Panksepp, 2012).

The neural architecture of the SEEKING system is deeply conserved in evolution (Huber, Panksepp, Nathaniel, Alcaro, & Panksepp, 2011). In mammals, dopamine (DA) transmission along the MFB, terminating in ventral striatal regions (e.g., nucleus accumbens), is an essential modulator of the overall SEEKING urge (Hills, Brockie, & Maricq, 2004; Panksepp, 1998). Thus, the SEEKING disposition is promoted by DA transmission within intermediary "associative" subcortical neural areas connecting sensory and motor processing. Most such areas are part of the "olfactory-limbic lobe," where the affective value of external stimuli is translated into intentional behavioral patterns through learning (Mogenson, Jones, & Yim, 1980). The mesolimbic-dopamine (ML-DA) system of mammals connects midbrain and forebrain nuclei involved in the basic expression of the ancestral SEEKING urge with more recently evolved forebrain areas where internally generated drives are integrated with perceptual, cognitive, and visceral information. The ML-DA system is then a neurochemical bridge through which basic SEEKING urges are transformed, via learning, into larger and more complex SEEKING neurodynamics and ever more focused behavior patterns (Alcaro & Panksepp, 2011), with abundant implications for psychiatric disorders such as depression and mania (Coenen et al., 2011).

The neuroanatomy of SEEKING involves a complex architecture (Alcaro & Panksepp, 2011; Ikemoto, 2010) so far unclear in humans, even though the human MFB has recently been characterized with diffusion tensor imaging (Coenen, Panksepp, Hurwitz, Urbach, & Mädler, 2012). An important neuro-evolutionary aspect concerns the expression of SEEKING within the cortical–subcortical midline structures conceptualized as the "core self" (Northoff & Panksepp, 2008; Panksepp & Northoff, 2009) and the way the constituent organismic coherence integrating midline brain systems controls all basic emotional dispositions in accordance with internal visceral states and with past experiences. The notion of a "core self" and its relation to subcortical midline regions touches upon the notion of the self as developed by Damasio (1999, 2010). He distinguishes a core mental self associated with rather cortical regions from

a "proto-self" or bodily self as being related to neural activity in the subcortical regions. Our notion of core self avoids such strict dichotomy between subcortical and cortical regions as well as between mental and bodily notions of self. We would argue that neural activity already in the subcortical regions allows for the constitution of a mental self, a core self, which is then further extended in its spatiotemporal coordinates by the contributions from the cortical regions. Accordingly, our notion of core self is reminiscent of Damasio's concept of "core or mental self" while at the same time being different by not adhering to the dichotomy between mental and bodily self (see also Northoff, Pengmin, & Feinberg, 2010; Qin & Northoff, 2011).

Recent human data have demonstrated that the SEEKING brain circuitry, as predicted, is involved in the emergence of a characteristic appetitive affective state, which may be described as normal "enthusiastic positive excitement" or "euphoria" (Drevets et al., 2001; Volkow & Swanson, 2003) all the way to mania (Coenen et al., 2009), which are feelings that do not resemble any kind of sensory pleasure (Alcaro & Panksepp, 2011; Heath, 1996). This has also been clear in relevant human studies of deep brain stimulation deployed in treatment resistant depression (Coenen et al., 2011; Schlaepfer et al., 2008).

We also note that the SEEKING system is the largest and most universally important of all the primal emotional systems, a system that is clearly involved in the positive emotions such as LUST, CARE, and PLAY, and is likely to also participate in the negative emotions, as in the seeking of safety in FEAR, which may reflect a secondary learning process (see Panksepp & Biven, 2012). In our estimation, such interactions do not compromise the importance of conceptualizing this primary-process emotion in its own terms as well as relations to psychiatric problems (see Wright & Panksepp, 2012, for extensive discussions). The neuroanatomies of these systems are extensively summarized elsewhere (Panksepp, 1998, 2005), and the trajectories of the SEEKING system in animals have been described in Ikemoto and Panksepp (1999), Ikemoto (2010), and Wright and Panksepp (2012), as well as recently in humans (Coenen et al., 2012). Briefly, the core of the system, constituted within the MFB, highlighted by the ascending mesolimbic dopamine system, extends both monosynaptically from the ventral tegmental area throughout the lateral hypothalamus, into various major terminal regions, especially nucleus accumbens and medial frontal cortical regions, and polysynaptically to many limbic cortical regions.

It is critical to note that although there are abundant anatomical candidates for the main part of the system, which has traditionally been called "the brain reward system" (basically a hand-me-down concept, from the behaviorist concept of generalized reward, without psychological contents), the SEEKING view is one that is based more on a direct analysis of the behaviors evoked by deep brain stimulation of these "reward" sites, which yield generalized exploratory and foraging patterns that contribute to the acquisition of all specific rewards needed for survival (Panksepp, 1981, 1998, 2005) as well as in human creativity. The utility and better conceptual clarity of the generalized positive hedonic SEEKING concept are thoroughly discussed in the above papers and are contrasted with related modern views elsewhere (Panksepp & Moskal, 2008; Wright & Panksepp, 2012).

The translation of this work to human investigations has just started (Coenen et al., 2012), but it should again be emphasized, from human Deep Brain Stimulation (DBS) studies, that this system is not involved in generating clearly rewarding pleasurable feelings, but rather enthusiasm for productive life-sustaining activities (e.g., Schlaepfer et al., 2008), even producing mania at high stimulation levels (Coenen et al., 2009). The relationship of this knowledge to understanding of a generalized anhedonia, engendered by various basic emotion interaction (e.g., chronic overactivity of the PANIC system), which leads to a lack of enthusiasm for life activities, is extensively discussed elsewhere (Coenen et al., 2012; Coenen et al., 2011; Panksepp & Watt 2011, 2012; Watt & Panksepp, 2009).

In sum, various other recent studies suggest a close relationship between emotional deficiency and dysfunction in the SEEKING disposition in human depression (Alcaro & Panksepp, 2011; Northoff, 2011; Northoff & Hayes, 2010; Zellner, Watt, Solms, & Panksepp, 2011; see also Koenigs et al., 2008, and Schlaepfer et al., 2008, for involvement of subcortical and cortical midline regions in depression), as well as across species (Alcaro, Panksepp, Witczak, Hayes, & Northoff, 2010). Northoff and Hayes (2010) have integrated human and animal data of depressive-like behaviors that show increased resting state activity in midline regions, along the anatomical trajectory of the SEEKING system, which are also implicated in self-specificity and reward-related processing. Reduced responding of reward-related and self-specific areas to positive stimuli in depressed subjects has also been noted and is in line with the increase in self-focus,

or ruminations, seen in this disorder. All this is in accord with the brain midline resting-state hypothesis of depression (Hasler & Northoff, 2011; Northoff, Wiebking, Feinberg, & Panksepp, 2011). Actually, the resting-state abnormalities in depression have been shown to be located in subcortical and cortical midline regions like the dorsomedial thalamus, the Periaqueductal Grey (PAG), and the perigenual anterior cingulate cortex in both human depression and animal models of depression (Alcaro et al., 2010; Northoff et al., 2011). Since one may assume the SEEKING to be the behavioral correlate of the brain's intrinsic activity in these and other especially subcortical midline regions, abnormalities in the latter naturally entail abnormal expression of the former (see Panksepp & Watt, 2011). Our lesion study lends some indirect support to the relationship between SEEKING and midline neural activity, though future studies are needed to demonstrate abnormalities in resting-state activity in these lesion patients.

While neuroanatomical circuitry underlying SEEKING in animals was studied for many years, its exact anatomical underpinnings in humans have remained unclear until recently (Coenen et al., 2012). Further, evidence from many of the specific brain lesions that were used in the past in attempts to ameliorate treatment-resistant depressive symptoms does suggest a convergence on the MFB trajectory of the SEEKING system (Schoene-Bake et al., 2010). This once more clearly indicates how powerfully upper brain processes, from frontal neocortex to nearby paralimbic regions, can regulate lower brain functions, which has become a general tenet of the neural analysis of human emotions (for reviews, see Davidson, Scherer, & Goldsmith, 2003; Lane & Nadel, 2000; Lewis, Haviland, & Barrett, 2008), with diverse views that are open for synthesis (Zachar & Ellis, 2012). Another major step in this direction would be to investigate alterations of SEEKING in patients with lesions in different locations of the brain.

The general aim of our exploratory study was to investigate the effect of brain lesions on behavioral measures of SEEKING and depression (Alcaro & Panksepp, 2011; Alcaro et al., 2010; Northoff et al., 2011; Panksepp & Watt, 2012; Watt & Panksepp, 2009; Zellner et al., 2011). More specifically, we aimed to investigate SEEKING in a group of stroke patients and a group of non-brain-lesioned control subjects. We hypothesized that patients with anterior and medial subcortical lesions, including extensions into cortical regions, comprising the entire limbic system, are central in leading to deficits in measures of both SEEKING and depression.

METHOD

The study group (stroke patients)

The present study was carried out across a span of two years. Sixty-two stroke inpatients in the acute phase were recruited after written informed consent. They came from a stroke unit to a rehabilitation hospital after the stabilization of the clinical situation (15 days to 1 month after the acute event). The communication of the diagnosis to the patient was managed by the stroke-unit doctors before their admission to the rehabilitation hospital.

Exclusion criteria included the presence of aphasia as measured with the Token Test (De Renzi & Faglioni, 1978; Spinnler & Tognoni, 1987; Zaidel, 1977) shown by a score lower than 26. Patients with MMSE (Mini-Mental State Examination) scores (Folstein, Folstein, & McHugh, 1975) of less than 21, corresponding to moderate/high cognitive impairments, were excluded. Patients with previous stroke events or with concomitant neurologic disease (chronic, acute, or degenerative) were also excluded. In general, most of stroke patients finally included in the study were elderly, with a slight prevalence of women (about 58% of the group).

In the following analyses, several possible differences in stroke locations were considered. The lesion location was determined independently from clinical symptoms and psychological assessment by the same neuroradiologist on the basis of magnetic resonance imaging (MRI) or computed tomography (CT) scans obtained during the acute phase (Gallucci, Capoccia, & Catalucci, 2005). Four possible lesion locations were contrasted: right/left hemisphere (34 vs. 27 patients), anterior/posterior region (19 vs. 12 patients), medial/lateral region (39 vs. 10 patients), and cortical/subcortical regions (12 vs. 24 patients). Specifically, anterior and posterior lesion locations were designated based on locations with respect to the sensorimotorial cortex. Participants with "cortical lesions" were based on damage restricted to cerebral gyrus and sulcus areas, while "subcortical lesions" were restricted to damage below cerebral cortex. "Medial lesions" referred to damage that infringed on midline structures—namely, in subcortical regions typically involving basal ganglia, while, at the cortical level, typically involving cingulate gyrus. "Lateral lesions" referred to brain damage restricted to areas starting far (at least 30 mm) from the midline.

It is worth noting that except in the case of right/left contrast, the number of cases considered in each comparison as a whole was considerably smaller than the total number of patients

actually included in the global sample: In fact, whenever lesions involved both brain regions/parts (e.g., bilateral lesion, etc.), patients were excluded from subsequent statistical analysis.

The control group (orthopedic patients)

In addition to the stroke group, we also recruited subjects for a control group of comparable age and clinical history. Thus, in order to exclude possible differences in reactive emotional states, we matched our control group with stroke patients on the following basic features: age, duration of hospitalization, and recency of traumatic events. Thus 76 orthopedic patients were selected as a control group that were affected by a recent leg bone fracture. These patients came from an orthopedic unit and were treated in the same rehabilitation hospital as the stroke patients.

An overall exclusion criterion was patients having MMSE scores less than 21. There was a prevalence of women (78% of the group). Most participants were married (39%) or widowed (45%), with only a small fraction never married (9%) or divorced (7%). Most subjects were retired (76%) with a minority still employed (18%) or active housewives (6%). Educational level was only slightly higher than that in the brain-damaged group.

Psychometric and psychiatric evaluations

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983, provided in the Italian version by Costantini et al., 1999) is a self-report rating scale designed to estimate levels of both anxiety and depression in hospitalized subjects. It consists of two subscales (HADS-Depression and HADS-Anxiety), each containing seven items on a 4-point Likert scale (ranging from 0–3). The HADS is scored by summing the ratings for the 14 items to yield a total score and by summing the ratings for the 7 items of each subscale to yield separate scores for anxiety and depression. HADS-Depression subscale was considered to evaluate depression. The validity of this instrument to measure depression and its equivalence to alternative tools (e.g., Beck Depression Inventory; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was determined in a number of studies involving patients with different pathologies, including stroke (Aben, Verhei, Lousberg, Lodder, & Honig, 2002; Loosman, Siegert, Korzec, & Honig, 2010; Preljevic et al., 2012; Sagen et al., 2009). In the Italian validation study (Costantini et al., 1999), the major depression results yielded an average HADS-Depression score of 8.3 ($SD = 3.5$).

The Affective Neuroscience Personality Scales (ANPS; Davis et al., 2003; with an Italian version provided by Andrea Clarici, University of Trieste, by personal communication, 2007) is a self-report questionnaire and includes three subscales concerning positive emotions (ANPS-SEEKING, ANPS-PLAY, and ANPS-CARE) and three negative emotions (ANPS-FEAR, ANPS-ANGER, and ANPS-SADNESS). Finally, an ANPS-Spirituality scale was introduced, focusing on feelings of connectedness with all of life and oneness with creation.

The whole questionnaire is composed of 110 items, grouped in seven scales with each basic affect evaluated by 14 items (7 of which are positively scored, and 7 negatively scored, see Davis & Panksepp, 2011, p. 1956).The Spirituality scale consists of only 12 items. There are various "filler items" to evaluate for deception and other potential issues of interest (which were not analyzed here). Items considered to evaluate SEEKING (i.e., relative to the ANPS-SEEKING subscale) are reported in Table 1. Administration of all tests was performed within the first week after admission by trained psychologists working in the rehabilitation hospital. Despite the fact that in the present study only HADS-Depression and ANPS-SEEKING subscales were of concern, both questionnaires were administrated in their complete form, to avoid possible biases.

In order to evaluate the degree of disability of our patients, the Functional Independence Measure (FIM) by Dodds, Martin, Stolov, and Deyo (1993) was administered by physiatrists within one week from enrolment in the study. Lower FIM scores indicate more functional deficits. Overall, FIM was administrated to 61 stroke patients out of 62 and to 69 orthopedic patients out of 76.

STATISTICAL ANALYSIS

Statistically significant differences between control and patient groups for possible covariates (age, gender, education, marital status, and occupation) were evaluated with t tests and chi-square comparisons, with a significance threshold of .05. The two groups did not differ except with regard to gender: Marginally more females were in the control group.

Differences in the average scores obtained by the various groups of patients with respect to the considered variates (ANPS-SEEKING, HADS-Depression, and FIM scores) were estimated by an analysis of variance (ANOVA). Since the original

TABLE 1
ANPS-SEEKING items

ANPS-SEEKING items	*Item no.*
Almost any little problem or puzzle stimulates my interest	1
I do not get much pleasure out of looking forward to special events	9
I really enjoy looking forward to new experiences	17
I like to set very practical goals rather than grandiose plans	25
Seeking an answer is as enjoyable as finding the solution	33
I often feel little eagerness or anticipation when thinking about my goals	41
I enjoy anticipating and working towards a goal almost as much as achieving it.	49
I am usually not interested in solving problems and puzzles just for the sake of solving them	57
My curiosity sometimes drives me to do things that others might consider a waste of time	65
I rarely feel the need just to get out and explore things	73
Whenever I am in a new place, I like to explore the area and get a better feel for my surroundings	81
I am not the kind of person that likes probing and investigating problems	89
I often feel like I could accomplish almost anything	97
I am not an extremely inquisitive person	105

Note. Davis et al., 2003. ANPS = Affective Neuroscience Personality Scales.

studies on healthy individuals (Davis et al., 2003) found significant sex differences in the average scores of some ANPS subscales, this possible biasing feature was accounted for by considering sex as a covariate in the ANOVA analysis. Whenever significant F ratios ($p < .05$) were obtained, post hoc t tests in the Tukey's form were used to determine specific effects on the considered scale.

Based on the overall above-mentioned group results, we correlated both the dimensions of ANPS-SEEKING and HADS-Depression with each other as well as with the FIM (the functional independence measure). Pearson correlation was used as follows: z-transformed correlation values were considered significant when the null hypothesis could be rejected at a significance level lower than 5% with a two-tailed test.

RESULTS

ANPS-SEEKING scores in lesion patients

Comparison between the two groups (stroke, control) revealed that ANPS-SEEKING scores were significantly lower in stroke patients than in the control group: Average scores for stroke and orthopedic patients were 32.74 ($SD = 5.69$) and 34.87 ($SD = 5.28$), respectively. Since analyses considered the gender as a covariate, it is unlikely that these differences are due to gender.

Impact of lesion location on ANPS-SEEKING scores

Marked differences in ANPS-SEEKING average scores appear in the different subgroups (Table 2). In particular, average ANPS-SEEKING scores in left, anterior, medial, and subcortical subgroups appear systematically lower than those in right, posterior, lateral, and cortical subgroups, but these differences were not statistically significant. Clearer statistical results emerged when stroke subgroups were compared with the control group. Anterior, medial, and subcortical lesions led to significantly lower ANPS-SEEKING scores than posterior, lateral, and cortical lesions.

ANPS-SEEKING and HADS-Depression

HADS-Depression scores were significantly higher in the stroke group, with respective average scores being 9.98 ($SD = 3.84$) and 7.95 ($SD = 4.13$). For the HADS-Depression scores, patients with anterior lesions exhibited significantly higher scores than those with posterior lesions. Patients with anterior, subcortical, and medial lesions also showed significantly higher scores than the control group (Table 2). ANPS-SEEKING scores were significantly negatively correlated with the HADS-Depression scores: The higher the ANPS-SEEKING scores, the lower the HADS-Depression scores. This holds for both lesion and control subjects (respective correlation coefficients $-.39$ and $-.31$; Figure 1).

DISCUSSION AND CONCLUSION

We report for the first time a behavioral study on the personality trait of SEEKING in humans that explores the impact of different lesion locations in human subjects. Our results show the following: (a) significant lower scores in ANPS-SEEKING in

TABLE 2
Comparison of average scores and respective standard deviations obtained in stroke patients grouped by the region of the lesion on the ANPS and HADS

	Anterior (A) (N = *19*)		*Posterior (P)* (N = *12*)		*Significance*		
	Average	SD	*Average*	SD	*A vs. P*	*A vs. CG*	*P vs. CG*
ANPS-SEEKING^	***30.42***	6.09	34.42	6.30	.09^	**<.01**	.80
HADS-Depression	***11.53***	3.31	8.17	4.09	**.02**	**<.01**	.83
FIM	***60.32***	15.17	***67.25***	*17.37*	.25	**<.01**	**.04**
	Cortical (C) ($N = 12$)		Subcortical (S) ($N = 24$)		Significance		
	Average	*SD*	Average	*SD*	C vs. S	C vs. CG	S vs. CG
ANPS-SEEKING	33.25	8.21	***31.88***	5.26	.55	.34	**.01**
HADS-Depression	9.75	4.77	***10.79***	3.70	.47	.15	**<.01**
FIM	***54.58***	16.98	***64.17***	13.65	.08	**<.01**	**<.01**
	Medial (M) ($N = 39$)		Lateral (L) ($N = 10$)		Significance		
	Average	*SD*	Average	*SD*	M vs. L	M vs. CG	L vs. CG
ANPS-SEEKING	***32.10***	5.79	34.20	6.63	.15	**<.01**	.72
HADS-Depression	***10.67***	3.74	9.40	4.95	.38	**<.01**	.30
FIM	***63.29***	16.38	*56.60*	14.83	.25	**<.01**	**<.01**
	Right (R) ($N = 34$)		Left (L) ($N = 27$)		Significance		
	Average	*SD*	Average	*SD*	R vs. L	R vs. CG	L vs. CG
ANPS-SEEKING	33.32	6.12	***31.96***	5.21	.36	.10	**.01**
HADS-Depression	***10.27***	3.66	***9.89***	3.95	.70	**<.01**	.03
FIM	***61.29***	*18.18*	***63.19***	***13.62***	.66	**<.01**	**<.01**

Note. ANPS = Affective Neuroscience Personality Scales. HADS = Hospital Anxiety and Depression Scale. FIM = Functional Independence Measure. Region of the lesion: anterior vs. posterior, cortical vs. subcortical, medial vs. lateral, right vs. left. The right three columns display the significance levels relative to the post hoc tests carried out between the two patient subgroups and between each subgroup and the control group (CG). Boldface indicates that, on the corresponding subscale, a significant ($p < .05$) difference exists between the two contrasted subgroups of patients, and the symbol "^" indicates that the difference is trending towards significance ($p < .1$). Boldface italic characters correspond to average scores that are significantly different ($p < .05$) from those in the control group.

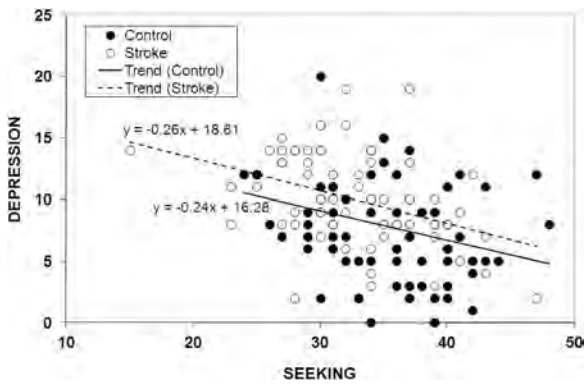

Figure 1. Scatter plot showing the correlation between ANPS-SEEKING and HADS-Depression scores of control (black circles) and stroke (empty circles) groups. ANPS = Affective Neuroscience Personality Scales. HADS = Hospital Anxiety and Depression Scale. Corresponding linear trends are also shown with the relevant regression equations.

patients with brain lesions; (b) significant impact of anterior, subcortical, and medial lesions on ANPS-SEEKING scores; (c) significant relationship of ANPS-SEEKING to HADS-Depression. Taken together, our results, though exploratory, suggest a significant role of anterior medial subcortical–cortical regions in SEEKING and its close relationship to depression.

The observed strong reduction of ANPS-SEEKING scores in the anterior, midline, and subcortical damage groups confirms how influential ancient regions of the brain are in regulating affective experiences (Panksepp, 1998). This is well in line with the findings in animals (Alcaro & Panksepp, 2011) where subcortical midline regions have been shown to play a central role in mediating SEEKING. Our observations extend this to humans, showing for the first time significantly lower ANPS-SEEKING scores (with respect to the

control group) in patients with lesions in these regions.

The anterior, medial, subcortical regions extend in humans to the anterior cortical midline structures like the ventromedial prefrontal cortex and the perigenual anterior cingulated cortex. Together they have therefore been subsumed under the concept of a subcortical–cortical midline system, thereby providing an anatomical bridge from animals to humans (Northoff & Panksepp, 2008; Panksepp & Northoff, 2009). The present study shows that the subcortical–cortical midline system may be not only anatomically relevant but also behaviorally, since it is associated with SEEKING as an intrinsic behavioral activation. However, future studies are needed to confirm the behavioral specificity of SEEKING associated with the anterior subcortical–cortical midline system. Moreover, the exact neuronal mechanisms need to be clarified. Given the fact that SEEKING is an intrinsic behavioral predisposition, one would expect that, neuronally, it may be related specifically to the intrinsic activity—that is, resting state activity—in these regions (see, for instance, Hasler & Northoff, 2011; Northoff et al., 2011; Qin & Northoff, 2011). However, this needs to be further tested in future studies.

In addition to SEEKING, our results show a clear relationship of the same regions with depression. This is well in accordance with recent observations showing abnormally high resting-state activity in subcortical–cortical midline regions in depression in both animal models and humans (see Alcaro, Panksepp, Witczak, Hayes, & Northoff, 2010; Northoff et al., 2011).

A recent lesion study by Koenigs et al. (2008) showed that ventromedial prefrontal cortical lesions reduced depressive symptoms, while lesions in dorsomedial and lateral prefrontal cortex were correlated with increased depressive symptoms. Our results cannot take a clear stance on this. Our lesions in the anterior midline extended through both ventro- and dorsomedial prefrontal cortex and sometimes also to lateral prefrontal regions. Hence, it remains unclear in our results whether the depressive symptoms are associated with either ventro- or dorsomedial prefrontal lesions.

In addition to the anterior and medial cortical lesions, our study supports the importance of subcortical midline limbic regions for depression. This is further supported by the absence of interaction between cortical lesions and depression. While this hints at the central role of subcortical regions for emotion and depression, as Panksepp argued (Panksepp, 1998, 2011a, 2011b, 2011c), future studies with patients showing exclusively subcortical lesions and exclusively cortical lesions would be necessary to better understand how they influence affective states. The assumed role of subcortical regions in the midline would also be in accordance with a recent report of the therapeutic effectiveness of deep brain stimulation in subcortical midline regions—for example, the nucleus accumbens, in depression (see Schlaepfer et al., 2008).

Finally, our results show significant correlation between SEEKING and depression: Higher scores in ANPS-SEEKING predicted lower scores in HADS-Depression. Interestingly, this holds true for both lesioned and nonlesioned subjects. This provides direct empirical evidence in favor of the suggested lowering of SEEKING in depression (Alcaro et al., 2010; Northoff et al., 2011; Panksepp & Watt, 2012; Qin & Northoff, 2011; Watt & Panksepp, 2009; Zellner et al., 2011).

Several limitations affect our study, making it exploratory in essence. First of all, the relatively small sample size was possibly responsible for the lack of statistical evidence for differences among brain-damaged subgroups (failing to pass the relevant statistical tests does not imply that hypothesized differences do not exist and based on the sample size may reflect a Type II error). Furthermore, it also prevented any further subdivision of the considered sample to better identify the role of the size of the lesion and of its specific location (e.g., by distinguishing among ventromedial, dorsomedial, or lateral lesion locations). This could be improved in future work through the application of more rigorous criteria than simply coarse lesion identification (e.g., voxel-based morphometry, perhaps applied concurrently with diffusion tensor imaging, DTI, of relevant brain circuits such as the MFB). Still, the encouraging findings we were able to harvest, despite relatively small sample size, prompts us, and hopefully others, to design future studies to address such shortcomings.

Another limitation we would address is the decision to include patients with relatively low MMSE scores ($\geq$21/30). Our decision was based on a clinical assessment of the actual possibility for subjects to actively participate in the evaluation. Clearly, as clinical experience has shown, even a slightly higher, perhaps more conventional, threshold ($\geq$24/30) does not exclude mild to moderate dementia. In any event, we cannot exclude possible biases induced by the declining motivation due to a multitude of interacting factors.

Another problematic aspect to be considered is the complex multifactorial character of poststroke depression where social (e.g., disability, lack of independence, recent negative life events, etc.) and psychological (e.g., personality traits, previous

history of depression, mourning processes, etc.) factors may play a significant role along with biological factors (Alexopoulos et al., 1997; Dafer, Rao, Shareef, & Sharma, 2008). These aspects, however, were not considered here. As an example, since diagnosis was communicated to each patient before their admission to the rehabilitation hospital where the present study was performed, we had no possibility of evaluating the eventual direct impact of how stroke diagnosis was actually managed and presented to the patient on eventual depressive status. Furthermore, the amplified vulnerability of stroke patients to prior depressive episodes was not considered here. These important aspects need to be addressed in future studies.

An unresolved critical aspect is the application of ANPS to target primary emotions: We must accept that SEEKING scale (and possibly all questionnaire scales) are assessing responses at a higher level of mental functioning. The difficulty of evaluating primary personality traits through tertiary cognitive abilities will remain in such patient populations, but future studies will also include measures other than just the ANPS and the HADS for SEEKING and depression, respectively, including more direct behavioral testing with explicit tasks requiring SEEKING behaviors. Of course such approaches can still only provide results representative of an integration of primary and higher brain functioning. As discussed by Coenen and colleagues (2012; Coenen et al., 2011) direct evaluation of primary brain structures and functions would require specific neurological procedures (e.g., "deep brain stimulation").

In conclusion, we have summarized findings from an extensive study of patients with distinct patterns of brain damage that show clear reductions of the basic dimension of SEEKING in left, medial, anterior, and subcortical lesions. Since almost the same pattern of psychological changes was obtained in depression scores, these findings further underline the central importance of both dimensions in the diminished neural processing of positive affective states in midline subcortical and anterior cortical brain regions. In this vein, it is also worth noting that deep-brain stimulation in the anterior regions of the SEEKING system, such as ventral striatum (i.e., nucleus accumbens), has been found to yield distinct and long-lasting antidepressant effects in treatment-resistant depressed human beings (Bewernick et al., 2010; Grubert et al., 2011; Schlaepfer et al., 2008). Further, considering the trajectory of the mesolimbic SEEKING system that feeds into the nucleus accumbens and medial frontal cortical regions, it is to be expected that even stronger antidepressant effects may be obtained by stimulating this medial forebrain bundle linked SEEKING system that has traditionally, and perhaps mistakenly, been called "the brain reward system" (Coenen et al., 2012; Coenen et al., 2011).

Original manuscript received 22 July 2012
Revised manuscript accepted 11 February 2013
First published online 1 March 2013

REFERENCES

Aben, I., Verhei, F., Lousberg, R., Lodder, J., & Honig, A. (2002). Validity of the Beck Depression Inventory, Hospital Anxiety and Depression Scale, SCL-90, and Hamilton Depression Rating Scale and screening instruments for depression in stroke patients. *Psychosomatics*, *43*, 386–393.

Alcaro, A., Huber, R., & Panksepp, J. (2007). Behavioral functions of the mesolimbic dopaminergic system: An affective neuroethological perspective. *Brain Research Reviews*, *56*, 283–321.

Alcaro, A., & Panksepp, J. (2011). The SEEKING mind: Primal neuro-affective substrates for appetitive incentive states and their pathological dynamics in addictions and depression. *Neuroscience and Biobehavioral Reviews*, *35*, 1805–1820.

Alcaro, A., Panksepp, J., Witczak, J., Hayes, D. J., & Northoff, G. (2010). Is subcortical cortical midline activity in depression mediated by glutamate and GABA? Across-species translational approach. *Neuroscience and Biobehavioral Reviews*, *3*, 592–605.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Kakuma, T., Silbersweig, D., & Charlson, M. (1997). Clinically defined vascular depression. *American Journal of Psychiatry*, *154*, 562–565.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–571.

Bewernick, B. H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., . . . Schlaepfer, T. E. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biological Psychiatry*, *67*, 110–116. doi:10.1016/j.biopsych.2009.09.01

Coenen, V. A., Honey, C. R., Hurwitz, T., Rahman, A. A., McMaster, J., Bürgel, U., & Madler, B. (2009). Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. *Neurosurgery*, *64*, 1106–1115. doi:10.1227/01.NEU.0000345631.54446.06

Coenen, V. A., Panksepp, J., Hurwitz, T. A., Urbach, H., & Mädler, B. (2012). Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): Imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. *Journal of Neuropsychiatry and Clinical Neurosciences*, *24*, 223–236.

Coenen, V. A., Schlaepfer, T. E., Maedler, B., & Panksepp, J. (2011). Cross-species affective functions and the medial forebrain bundle—Implications for the treatment of affective pain and depression in

humans. *Neuroscience and Biobehavioral Reviews*, *35*, 1971–1981.

Costantini, M., Musso, M., Viterbori, P., Bonci, F., Del Mastro, L., Garrone, O., . . . Marasso, G. (1999). Detecting psychological distress in cancer patients: Validity of the Italian version of the Hospital Anxiety and Depression Scale. *Supportive Care in Cancer*, *7*, 121–127.

Dafer, R. M., Rao, M., Shareef, A., & Sharma, A. (2008). Poststroke depression. *Topics in Stroke Rehabilitation*, *15*, 13–21. doi:10.1310/tsr1501-13

Damasio, A. (1999). *The feeling of what happens: Body and emotion in the making of consciousness*. New York, NY: Harcourt Brace.

Damasio, A. (2010). *Self comes to mind: Constructing the conscious brain*. New York, NY: Pantheon.

Davidson, R. J., Scherer, K. R., & Goldsmith, H. H. (2003). *Handbook of affective sciences*. New York, NY: Oxford University Press.

Davis, K. L., & Panksepp, J. (2011). The brain's emotional foundations of human personality and the Affective Neuroscience Personality Scales. *Neuroscience and Biobehavioral Reviews*, *35*, 1946–1958.

Davis, K. L., Panksepp, J., & Normansell, L. (2003). The Affective Neuroscience Personality Scales: Normative data and implications. *Neuropsychoanalysis*, *5*, 57–69.

De Renzi, E., & Faglioni, P. (1978). Normative data and screening power of a shortened version of the Token Test. *Cortex*, *14*, 41–49.

Dodds, T. A., Martin, D. P., Stolov, W. C., & Deyo, R. A. (1993). A validation of the functional independence measure and its performance among rehabilitation inpatients. *Archives in Physical Medicine and Rehabilitation*, *74*, 531–536.

Drevets, W. C., Gautier, C., Price, J. C., Kupfer, D. J., Kinahan, P. E., Grace, A. A., . . . Mathis, C. A. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biological Psychiatry*, *49*, 81–96.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychosomatic Research*, *12*, 189–198.

Gallucci, M., Capoccia, S., & Catalucci, A. (2005). *Radiographic atlas of skull and brain anatomy*. Berlin: Springer-Verlag Berlin and Heidelberg GmbH & Co.

Grubert, C., Hurlemann, R., Bewernick, B. H., Kayser, S., Hadrysiewicz, B., Axmacher, N., . . . Schlaepfer, T. E. (2011). Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: Effects of 12-month stimulation. *World Journal of Biological Psychiatry*, *12*, 516–527. doi:10.3109/15622975.2011.583940

Hasler, G., & Northoff, G. (2011). Discovering imaging endophenotypes for major depression. *Molecular Psychiatry*, *16*, 604–619.

Heath, R. C. (1996). *Exploring the mind–body relationship*. Baton Rouge, LA: Moran Printing.

Hills, T., Brockie, P. J., & Maricq, A. V. (2004). Dopamine and glutamate control area restricted search behavior in Caenorhabditis elegans. *Journal of Neuroscience*, *24*, 1217–1225. doi:10.1523/JNEUROSCI.1569-03

Huber, R., Panksepp, J. B., Nathaniel, T., Alcaro, A., & Panksepp, J. (2011). Drug sensitive reward in crayfish: An invertebrate model system for the study of SEEKING, reward, addiction, and withdrawal. *Neuroscience and Biobehavioral Reviews*, *35*, 1847–1853. doi:10.1016/j.neubiorev.2010.12.008

Ikemoto, S. (2010). Brain reward circuitry beyond the mesolimbic dopamine system: A neurobiological theory. *Neuroscience and Biobehavioral Reviews*, *35*, 129–150.

Ikemoto, S., & Panksepp, J. (1999). The role of nucleus accumbens dopamine in motivated behavior: A unifying interpretation with special reference to reward-seeking. *Brain Research Reviews*, *31*, 6–41.

Koenigs, M., Huey, E. D., Calamia, M., Raymont, V., Tranel, D., & Grafman, J. (2008). Distinct regions of prefrontal cortex mediate resistance and vulnerability to depression. *Journal of Neuroscience*, *28*, 12341–12348.

Lane, R. D., & Nadel, L. (2000). *Cognitive neuroscience of emotions*. New York, NY: Oxford University Press.

Lewis, M., Haviland, J. M., & Barrett, L. F. (Eds.). (2008). *Handbook of emotions* (3rd ed.). New York, NY: Guilford.

Loosman, W. L., Siegert, C. E. H., Korzec, A., & Honig, A. (2010). Validity of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory for use in end-stage renal disease patients. *British Journal of Clinical Psychology*, *49*, 507–516.

Mogenson, G. J., Jones, D. L., & Yim, C. Y. (1980). From motivation to action: Functional interface between the limbic system and the motor system. *Progress in Neurobiology*, *14*, 69–97. doi:10.1016/S0165-0173(99)00023-5

Northoff, G. (2011). *Neuropsychoanalysis in practice*. New York, NY: Oxford University Press.

Northoff, G., & Hayes, D. J. (2010). Is our self nothing but reward? *Biological Psychiatry*, *69*, 1019–1025. doi:10.1016/j.biopsych.2010.12.014

Northoff, G., & Panksepp, J. (2008). The trans-species concept of self and the subcortical–cortical midline system. *Trends in Cognitive Sciences*, *12*, 259–264.

Northoff, G., Pengmin, P., & Feinberg, T. E. (2010). Brain imaging of the self—Conceptual, anatomical and methodological issues. *Consciousness and Cognition*, *20*, 52–63. doi:10.1016/j.concog.2010.09.011

Northoff, G., Wiebking, C., Feinberg, T., & Panksepp, J. (2011). The "resting-state hypothesis" of major depressive disorder—A translational subcortical–cortical framework for a system disorder. *Neuroscience and Biobehavioral Reviews*, *35*, 1929–1945.

Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative & Physiological Psychology*, *47*, 419–427.

Panksepp, J. (1981). Hypothalamic integration of behavior: Rewards, punishments and related psychobiological process. In P. J. Morgane & J. Panksepp (Eds.), *Handbook of the hypothalamus: Part A. Behavioral studies of the hypothalamus* (Vol. 3, pp. 289–487). New York, NY: Marcel Dekker.

Panksepp, J. (1982). Toward a general psychobiological theory of emotions. *Brain Research Reviews*, *5*, 407–467.

Panksepp, J. (1998). *Affective neuroscience: The foundations of human and animal emotions*. New York, NY: Oxford University Press.

Panksepp, J. (2005). Affective consciousness: Core emotional feelings in animals and humans. *Consciousness and Cognition*, *14*, 19–69.

Panksepp, J. (2011a). Cross-species affective neuroscience decoding of the primal affective experiences of humans and related animals. *Public Library of Science One*, *6*, e21236. doi:10.1371/journal.pone.0021236

Panksepp, J. (2011b). The neurobiology of social loss in animals: Some keys of the puzzle of physic pain in humans. In L. A. Jensen-Campbell & G. MacDonald (Eds.), *Social pain: Neuropsychological and health implication of loss and exclusion* (pp. 11–51). Washington, DC: American Psychological Association.

Panksepp, J. (2011c). Toward a cross-species neuroscientific understanding of the affective mind: Do animals have emotional feelings? *American Journal of Primatology*, *73*, 545–561. doi:10.1002/ajp.20929

Panksepp, J., & Biven, L. (2012). *The archaeology of mind: Neuroevolutionary origins of human emotions*. New York, NY: W. W. Norton & Company.

Panksepp, J., & Moskal, J. (2008). Dopamine and SEEKING: Subcortical "reward" systems and appetitive urges. In A. Elliot (Ed.), *Handbook of approach and avoidance motivation* (pp. 67–87). New York, NY: Taylor & Francis.

Panksepp, J., & Northoff, G. (2009). The trans-species core SELF: The emergence of active cultural and neuro-ecological agents through self-related processing within subcortical–cortical midline networks. *Consciousness and Cognition*, *18*, 193–215.

Panksepp, J., & Watt, J. (2011). Why does depression hurt? Ancestral primary-process separation-distress (PANIC) and diminished brain reward (SEEKING) processes in the genesis of depressive affect. *Psychiatry*, *74*, 5–14.

Panksepp, J., & Watt, D. (2012). Why does depression hurt? Ancestral primary-process separation-distress (PANIC/GRIEF) and diminished brain reward (SEEKING) processes in the genesis of depressive affect. *Psychiatry*, *74*, 5–13.

Preljevic, V. T., Østhus, T. B. H., Sandvik, L., Opjordsmoen, S., Nordhus, I. H., Os, I., & Dammen, T. (2012). Screening for anxiety and depression in dialysis patients: Comparison of the Hospital Anxiety and Depression Scale and Beck Depression Inventory. *Journal of Psychosomatic Research*, *73*, 139–144.

Qin, P., & Northoff, G. (2011). How is our self related to midline regions and the default-mode network? *NeuroImage*, *57*, 1221–1233. doi:10.1016/j.neuroimage.2011.05.028

Sagen, U., Vik, T. G., Moum, T., Mørland, T., Finset, A., & Dammen, T. (2009). Screening for anxiety and depression after stroke: Comparison of the Hospital Anxiety and Depression Scale and the Mongomery and Åsberg Depression Rating Scale. *Journal of Psychosomatic Research*, *67*, 325–332.

Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., . . . Sturm, V. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*, *33*, 368–377.

Schoene-Bake, J. C., Parpaley, Y., Weber, B., Panksepp, J, Hurwitz, T. A., & Coenen, V. A. (2010). Tractographic analysis of historical lesion surgery for depression. *Neuropsychopharmacology*, *35*, 2553–2563. doi:10.1038/npp.2010.132

Spinnler, H., & Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici [Italian Standardization and Calibration of Neuropsychological Tests]. *Italian Journal of Neurological Sciences*, *8*, 1–120.

Volkow, N. D., & Swanson, J. M. (2003). Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *American Journal of Psychiatry*, *160*, 1909–1918. doi:10.1176/appi.ajp.160.11.1909

Watt, D. F., & Panksepp, J. (2009). Depression: An evolutionarily conserved mechanism to terminate separation-distress? A review of aminergic, peptidergic, and neural network perspectives. *Neuropsychoanalysis*, *11*, 7–51.

Wright, J. S., & Panksepp, J. (2012). An evolutionary framework to understand foraging, wanting, and desire: The neuropsychology of the SEEKING system. *Neuropsychoanalysis*, *14*, 5–39.

Zachar, P., & Ellis, R. (Eds.). (2012). *Emotional theories of Jaak Panksepp and Jim Russell*. Amsterdam: John Benjamins.

Zaidel, E. (1977). Unilateral auditory language comprehension on the Token Test following cerebral commissurotomy and hemispherectomy. *Neuropsychologia*, *15*, 1–18.

Zellner, M. R., Watt, D. F., Solms, M., & Panksepp, J. (2011). Affective neuroscientific and neuropsychoanalytic approaches to two intracTab psychiatric problems: Why depression feels so bad and what addicts really want. *Neuroscience and Biobehavioral Reviews*, *35*, 2000–2008.

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*, 361–370.