Intact alternation performance in high lethality suicide attempters

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ABSTRACT

Suicide attempters often perform poorly on tasks linked to ventral prefrontal cortical (VPFC) function. Object Alternation (OA) – a VPFC probe – has not been used in these studies. In this study, currently depressed medication-free past suicide attempters whose most severe attempt was of high ($n=31$) vs. low ($n=64$) lethality, 114 medication-free depressed non-attempters, and 86 non-patients completed a computerized OA task. Participants also completed comparison tasks assessing the discriminant validity of OA (Wisconsin Card Sort), its concurrent validity relative to tasks associated with past attempt status (computerized Stroop task, Buschke Selective Reminding Test), and its construct validity as a VPFC measure (Go-No Go and Iowa Gambling Task). Against expectations, high lethality suicide attempters – the majority of whom used non-violent methods in their attempts with some planning – outperformed other depressed groups on OA, with no group differences observed on Wisconsin Card Sort. Despite intact performance on OA, past attempters exhibited deficits on the Stroop and Buschke. OA performance was associated with performance on Go-No Go and Iowa Gambling, confirming that OA measures a similar construct. VPFC dysfunction may not be a characteristic of all suicide attempters, especially those who make more carefully planned, non-violent – though potentially lethal – attempts.

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1. Introduction

Neural circuitry involving ventral prefrontal cortex is central to a number of neuropsychological models of suicidal behavior, for compelling reasons. Damage to ventral prefrontal, especially orbitofrontal, cortex can result in the type of impulsive aggressive behavior (Best et al., 2002) that is a significant risk factor for suicidal behavior in the context of psychiatric illness (Dumais et al., 2005; McGirr and Turecki, 2007; Gvion and Apter, 2011). Serotonin receptor and transporter abnormalities have been found in ventrolateral and orbitofrontal cortex in post-mortem studies of suicide completers (Arango, et al., 1997; Arango et al., 2002; Underwood et al., 2012). Deficits in language fluency and non-verbal design fluency, associated with left and right inferior prefrontal functions respectively, have been found in past suicide attempters (Bartfai et al., 1990). In our own work, high lethality suicide attempters exhibited deficits in both language fluency and a secondary measure from the Wisconsin Card Sort (failure to maintain; Keilp et al., 2001) that is sensitive to ventral prefrontal dysfunction (Stuss et al., 2000).

More recent studies have found deficits in suicide attempters on a variety of measures sensitive to VPFC dysfunction, including gambling tasks, impulse control tasks, and probabilistic reversal learning. The Iowa Gambling Task (Bechara et al., 1994; Bechara, 2007) is a decision-making task that is sensitive to damage in this cortical region (Bechara et al., 2000) and produces VPFC activation (Li et al., 2010; Lawrence et al., 2009). IGT deficits have been found in past attempters who have used violent methods in their attempts (Jollant et al., 2005), as well as in past attempters from mixed diagnostic groups (Jollant et al., 2007). IGT deficits have been found in attempters with suicidal ideation that persists after an attempt (Westheide et al., 2008), although IGT deficits have not been found in all studies of suicidal behavior (Legris et al., 2012; Gorlyn et al., 2013) or self-harm (Janis and Nock, 2009). Suicide attempters have performed poorly on impulse control tasks in a number of studies (Swann et al., 2005; Wu et al., 2009, Dougherty et al., 2009). Elderly suicide attempters have performed poorly on both the Cambridge Gambling Task (Clark et al., 2011) and probabilistic reversal learning (Dombrovski et al., 2010) – the latter well-validated in both human and animal studies with regard to their association with VPFC function (Clark et al., 2004).

One task sensitive to VPFC dysfunction that has not been used in studies of suicide attempters is Object Alternation (OA), a task requiring both mental flexibility and set maintenance for optimal performance. Given our own earlier findings (Keilp et al. 2001) and

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those of recent studies suggesting VPFC dysfunction in past suicide attempters, OA should – like other tasks sensitive to VPFC dysfunction – be impaired in past attempters.

The OA paradigm was first developed for use in primate lesion studies as an extension of the delayed match-to-sample and delayed alternation paradigms, and was specifically sensitive to VPFC damage in these primate studies (Pribram and Mishkin, 1956; Mishkin et al., 1969). The task involves baiting one of two distinct objects with a reward, and requiring the subject to learn that the reward will be moved to the opposite object, regardless of location, whenever reward is obtained. The original primate task was adapted for use in humans by Freedman et al. (1998), who found higher error rates in depressed subjects than healthy volunteers. Computerized versions of the task were later developed in various laboratories for use in both clinical (Blair et al., 2006; González-Blanch et al., 2008) and imaging (Zald et al., 2005) studies. Functional imaging studies have confirmed its association to VPFC function (Gold et al., 1996; Zald et al., 2005).

We had previously reported initial results from this study (71.0% of current samples; Keilp et al., 2013) and were surprised to find that the highest lethality attempters made fewer errors than lower lethality attempters, contrary to our initial hypotheses. This report is based on an expanded sample given the potential theoretical importance of this finding. It provides greater detail about object alternation performance via its various subscores, and examines its relationship to other measures that assess abstraction abilities, that differentiate past suicide attempters, and that are related to putative VPFC dysfunction. Medication-free, depressed individuals with and without a history of suicidal behavior – as well as a sample of healthy volunteers – were administered a computerized object alternation task as part of an extensive clinical assessment.

This assessment included the Wisconsin Card Sorting Task (WCST), an executive performance measure more closely associated with dorsolateral prefrontal dysfunction (Stuss et al., 2000). The WCST was included in order to examine the potential discriminant validity of OA with respect to suicidal behavior, following the rationale of Abbruzzese et al. (1997) who used these tasks to characterize differential deficits in schizophrenia (more impaired on WCST) and obsessive-compulsive disorder (more impaired on OA). A relative deficit in OA performance was expected based on studies cited above; few consistent differences in WCST performance have been found in past attempters (Jollant et al., 2011). In the original design for this study, then, we hypothesized that OA – and not standard measures from the WCST – would be associated with past suicide attempt.

To examine the possible concurrent validity of OA with respect to its sensitivity to suicidal behavior, OA performance was also compared to two tasks that have consistently discriminated past attempters in our studies – a computerized Stroop task and the Buschke Selective Reminding Test (Keilp et al., 2001, 2008, 2013; Richard-Devantoy et al., 2013). If OA deficits were characteristic of suicide attempters, we would also expect poor OA performance to be associated with these other deficits found in past attempters.

Finally, the construct validity of OA was examined by comparing performance on this task to that on other tasks associated with VPFC dysfunction, that were acquired in subgroups of the total sample. Presumably, all of these tasks are sensitive to dysfunction associated with VPFC, the broad "construct" of interest. OA performance was compared to performance on the Iowa Gambling Task and a Go-No Go task, both of which have been associated with VPFC function in both lesion and imaging studies (Zald and Andreotti, 2010).

Past attempters were divided for analyses into those who had made less vs. more lethal attempts, based on our earlier findings (Keilp et al., 2001) and our initial hypothesis that OA deficits would be most pronounced in those who had made the most severe past attempts.

2. Methods

2.1. Subjects

Patients were 209 medication-free individuals in a major depressive episode (both unipolar and bipolar), including 114 who had never attempted suicide and 95 who had made at least one suicide attempt (defined as a self-injurious act with intent to die). Non-patient comparison group included 84 healthy volunteers with no major psychiatric illness. Suicide attempter sample was divided into low lethality ($n=64$) and high lethality ($n=31$) past attempters. Lethality of past attempts was determined using Beck's rating of medical damage (Beck et al., 1975), which ranges from zero (no injury) to eight (death). Low lethality attempts were maximally rated 3 (minor injury requiring routine medical intervention); high lethality attempts were minimally rated four (injury requiring major medical intervention). At the time of assessment, all participants were free of major medical and neurological illnesses by history and medical exam.

2.2. Instruments

2.2.1. Clinical Assessment

The Structured Clinical Interview for DSM-IV, Axes I (SCID-I; Spitzer et al., 1990) and II (SCID-II; First et al., 1996) was used to establish diagnoses in patient subjects. The non-patient version of the SCID (SCID-NP; First et al., 1997) was used to rule out psychiatric diagnoses in healthy comparison subjects. Other clinical ratings have been described previously (Mann et al., 1999) and are listed in Table 1.

The Vocabulary subtest from the Wechsler Adult Intelligence Scale, 3rd revision (WAIS-III; Wechsler, 1997) was used to estimate intellectual ability. The Columbia Suicide History (Oquendo et al., 2003) was used to characterize past suicidal behavior. Lethality of past suicide attempts was assessed via Beck's medical damage rating of physical injury resulting from an attempt (Beck et al. 1975). Scale ranges from zero (no physical damage) to eight (death). Attempts rated 3 or below (maximally, mild physical injury requiring medical intervention) were designated as low lethality; those 4 and above (minimally, serious injury requiring medical intervention) were designated as high lethality.

2.2.2. Object Alternation Task

The OA task was presented on a Macintosh Powerbook laptop computer and programmed in PsyScope (Cohen et al., 1993). Two symbols, a red triangle and a blue circle, were presented simultaneously on a computer screen, with either the triangle on the left or the triangle on the right (side of presentation determined in a pseudo-random fashion). Subjects were instructed to select the object that they thought was correct on any given trial, and told there was a pattern to determining which item was correct on any given trial. Subjects responded by keypress to designate the location of the object they were selecting. Correct responses were reinforced with a computer beep; incorrect responses received a buzz. The subject's first response, to either symbol, was correct by default. Thereafter, the opposite figure that the subject responded to correctly was designated as correct on the next trial. To respond correctly on each trial, then, the subject was required to alternate between the objects from trial to trial, regardless of which side the alternate object was presented on. Once an object was designated as correct, it remained correct until selected by the subject. Intertrial interval was 500 ms. The test was stopped if the subject made 12 correct responses in a row (12 alternations without an error). If the subject did not complete the test to criterion, it was discontinued after 180 presentations of the stimuli. Subjects were scored on their ability to reach the criterion of 12 correct in a row, on the number of errors made, on the number of perseverative errors (errors following errors), and on failures to maintain a response set (achieving 5 or more correct responses in a row and making an error before completing the test to criterion). Following Freedman et al. (1998), learning was characterized by calculating the number of errors for every set of 10 correct responses (in order to facilitate comparison across subjects, error scores for those who completed the test to criterion was set to zero for subsequent bins).

2.2.3. Wisconsin Card Sort

The Wisconsin Card Sort was administered to all subjects as a comparison measure, using the standard manual administration, to determine if deficits were specific to object alternation or affected abstraction abilities more globally. Abbruzzese et al. (1997) demonstrated that these tasks could be used to characterize differential deficits in schizophrenia (more impaired on WCST) and obsessive-compulsive disorder (more impaired on OA); a comparable strategy was employed here.

2.2.4. Computerized Stroop Task and Buschke Selective Reminding Test

Participants received an extensive battery of other neuropsychological measures, described elsewhere (Keilp et al., 2013). These tests included two measures that have consistently discriminated suicide attempters in our studies, a computerized Stroop task and the Buschke Selective Reminding task (Keilp et al., 2001, 2008, 2013). These measures were analyzed here to determine if suicide